Introduction

Fortunately, the current era is one in which a variety of medical and surgical innovations are in active development in renal cell carcinoma (RCC). From the medical side, the emphasis is on targeted therapies, with currently approved drugs that impact the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and Raf pathways, as well as mTOR protein expression. Furthermore, additional investigational applications including other growth-factor receptor tyrosine kinases and downstream proteins, as well as increasing complex immune manipulations, beyond cytokines, are similarly promising. From the surgical and locally directed therapy standpoint, technical novelties such as laparoscopic, robotic, and energy-intense modalities (radiofrequency ablation, cryoablation and potentially...
with high-intensity frequency ultrasound) increasingly demonstrate comparable nephron-preservation potential, with minimal morbidity, and comparable treatment-specific short-term outcomes. Definitive local control of the primary is always a goal in localized disease but is conceptually less important in the context of established metastatic disease where debulking is the primary goal. The psychologic impact of primary tumor resection is a further dimension in a patient’s decision-making process.

However, compelling prospective trials attribute a survival advantage to nephrectomy itself, in the face of metastatic disease. Among patients selected for suitability for nephrectomy despite radiographically evident metastatic disease, those assigned to nephrectomy followed by interferon treatment had a median survival of 13.6 months compared with 7.8 months in patients assigned to interferon alone. Similarly, from a retrospective outlook, nephrectomy status is a major factor in clinical prognostic stratification, along with performance status, hemoglobin level, serum calcium level, and lactate dehydrogenase (LDH) measurement. Other factors that were prognostic in the databases of the Southwest Oncology Group (SWOG) and the European Organisation for Research and Treatment of Cancer (EORTC) included Eastern Cooperative Oncology Group (ECOG) performance status, serum alkaline phosphatase level, and lung-only pattern of metastatic spread.

These experiences predate targeted drug availability for RCC. The extent to which these historical series parallel our treatment-specific outcomes with these novel agents is unclear. Similarly, the optimal integrations of these experiences were not evaluated directly against the new drugs. The optimal integration of surgery and medical therapy is yet to be elucidated. Nevertheless, clinical scoring systems identify good-risk subsets of patients significantly greater median survival (22 to 30 months) compared with the subjects in this nephrectomy trial, but the extent to which these data are applicable to patients already stratified is uncertain.

Patients with kidney cancer, particularly those with metastatic disease, are heterogeneous with respect to tumor histology, age at presentation, performance status, and anatomic pattern of spread. To whom should nephrectomy be offered? Before or after medical treatment, or permanently deferred? Should our experience with metastatic RCC, consisting predominantly of clear cell histology tumors (~ 75%), be extrapolated to the papillary RCC (10% to 15%) and the 12 rarer subtypes of kidney tumors defined in the 2004 WHO classification simply because they originate from the same organ of origin? How does the answer change with the introduction of the targeted drug era? A variety of clinical and laboratory parameters can help tailor the approach for an individual patient, leading to the central question of strategic integration of nephrectomy with targeted therapy for the patient with metastatic RCC at presentation.

With about one-third of incidentally detected kidney cancers being metastatic at presentation, as well as the presence of locally advanced disease, the issue of initial anticancer treatment by medical or surgical intervention is a frequent topic of discussion. Patients with stage IV disease, however, are a heterogeneous group, even after assignment to a risk stratification category. For some patients, the extent of metastatic disease is detectable but miniscule, or obvious symptoms are directly attributable to the primary tumor, such as hematuria and abdominal pain. The circumstances that contribute to an easy decision to consider upfront cytoreductive nephrectomy can be considered in two aspects: one is a general medical context of good reserve of renal function in the contralateral kidney (or in a noninvolved, salvageable component of the ipsilateral kidney); the other is data demonstrating survival advantage attributable to nephrectomy, from experience preceding the targeted drug era.

At the other extreme, compromising situations such as high relative metastatic bulk (compared to the primary), multiple medical comorbidities, frailty that raises operative and perioperative risk, histologic subtype that is not clear cell in which the majority of our clinical experience lies, or limitations on renal functional reserve, nephrectomy must be deferred either temporally or permanently.

What is the best approach for a fit patient, with a technically resectable primary tumor, who has metastatic disease? Will new agents control the primary to an extent that obviates the benefit attributable to cytoreductive nephrectomy? How are risk stratifications based on postnephrectomy patients relevant to a nephrectomy decision? Of specific concern, there is a middle ground, with a technically resectable primary tumor, good anticipated postsurgical renal functional reserve, and perhaps mild or moderate symptoms, possibly raising the question of a durable response with high-dose intravenous interleukin-2 (IL-2). What sequence strategy is optimal in this specific clinical scenario?

As the urologic oncology experience accumulates, more medical and surgical options — each of which individually has demonstrated oncologic benefits in terms of symptom-control, progression-free survival (PFS), and overall survival — the physician integrating a multidisciplinary treatment plan is faced with a treatment dilemma: can the benefit be increased through strategic sequencing and combinations? An empiric change in our treatment paradigm is naturally slower to develop than the identification of benefit in isolated drug-specific clinical trials. The decision of nephrectomy and metastatectomy vs medical treatment is a unique application of the sequencing question.

At present, factors that influence our decision about the initial therapy include ECOG performance prior to surgery, clinical characteristics of the tumor,
psychologic outlook of the patient about the operation, and expected perioperative morbidity and convalescence. As discussed below, the clinical factors that influence the individualized decision process are derived from a variety of independent experiences and challenge the multidisciplinary team to reach a personalized treatment decision algorithm.

**Prognostic Factors: Drug-Independent General Prognostic Stratification**

Intrinsic disease characteristics continue to be the predominant factors influencing survival patterns for many patients. These disease features are independent of treatment decisions; the heterogeneity of anatomic pattern of spread and tumor growth, as well as survival rates of the stage IV metastatic RCC patient, precludes a uniform recommendation for all RCC patients with metastatic disease. Established clinical and laboratory data derived from disease biology are predictive of disease-specific outcomes in RCC; these include clinical or pathologic TNM stage, Fuhrman grade, lymph node status, and metastatic status. Other factors, such as disease extension into veins of the renal sinus, might identify those at risk of metastatic disease progression, even if the tumor is confined to the kidney.

Among 670 metastatic RCC patients in phase II studies, factors that were predictive of survival included performance status, serum calcium level, serum hemoglobin level, serum LDH level, and nephrectomy status. For 251 previously treated patients, features that were identified as adverse included low performance status, low serum hemoglobin level, and high corrected serum calcium level. Other prognostic models, incorporating serum alkaline phosphatase level and number of metastatic level, have been developed, as well as surrogate prognostic tumor markers such as carbonic anhydrase 9 (CA9), p53, gelsolin, PTEN, and vimentin. The prognostic tumor markers identified in these experiences were mainly in patients treated with nephrectomy, so the validity of these conclusions among patients treated with targeted therapy has yet to be demonstrated. The prognostic implications of different anatomic sites of spread for patients on targeted drug therapy are a further area for study.

The prognostic factors cited and described above were utilized in the stratification, design, and selection of patients among the treatment arms for the pivotal clinical trial testing the merit of several therapeutic agents including sunitinib, sorafenib, bevacizumab, pazopanib, everolimus, and temsirolimus (Table). The same prognostic scoring systems are applied routinely in guidelines for the selection of novel systemic agents, including many targeted therapies and IL-2. A recent report demonstrating the feasibility of neoadjuvant bevacizumab followed by debulking nephrectomy also accent a shortcoming of the scoring system, focusing the attention onto the nephrectomy/debulking issue. In contrast to studies with mostly patients who have already had cytoreductive nephrectomy studies, where “good-risk” patients predominate (eg, one-half of patients in the sorafenib or sunitinib pivotal trials), none of the 52 patients in this series met the “good-risk” criteria at initial evaluation. Hence, this difference in the risk category distribution of patients imparts a

<table>
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<tr>
<th>Study Sponsor and Reference</th>
<th>Systemic Therapy</th>
<th>Population Sample Size (No. of Patients)</th>
<th>Nephrectomy Status</th>
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<tr>
<td>NCI11</td>
<td>Interleukin-2 (nonrandomized)</td>
<td>154</td>
<td>100% nephrectomy</td>
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<td>Nephrectomy plus interferon vs interferon alone</td>
<td>331</td>
<td>Randomized 1:1</td>
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<td>Bayer12</td>
<td>Sorafenib vs placebo</td>
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<td>94%</td>
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<td>Pfizer13</td>
<td>Sunitinib vs interferon</td>
<td>750</td>
<td>89% (of sunitinib arm)</td>
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<td>Pfizer14</td>
<td>Sunitinib expanded access</td>
<td>4,617</td>
<td>88%</td>
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<tr>
<td>Wyeth15,16</td>
<td>Temsirolimus vs interferon vs both</td>
<td>416 (counting temsirolimus only and interferon only)</td>
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<td>Everolimus vs placebo</td>
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<td>Bevacizumab + interferon vs interferon</td>
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<td>Required (100%)</td>
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<td>GlaxoSmithKline20</td>
<td>Pazopanib vs placebo</td>
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NCI = National Cancer Institute, SWOG = Southwest Oncology Group, EORTC = European Organisation for Research and Treatment of Cancer, CALGB = Cancer and Leukemia Group B.
limitation in applying the stratification for comparing the outcomes with other strategies.

**Merits of Regional Lymphadenectomy**

An important consideration in surgical planning is the preoperative assessment for the presence of regional lymphadenopathy. The prognostic importance of regional lymphadenopathy has been assessed by several groups. In a study by Vasselli et al from the National Cancer Institute, 154 patients with metastatic RCC underwent cytoreductive nephrectomy (with planned subsequent systemic II-2 adjuvant therapy). In this retrospectively collected cohort, the presence of metastatic RCC without preoperative lymphadenopathy was associated with a longer survival (median of 14.7 months vs median of 8.5 months in patients with preoperatively identified lymphadenopathy). Preoperatively identified lymphadenopathy was a more important prognostic indicator than patient performance status. In this same study, the authors demonstrated that unresectable nodal metastasis portended a worse prognosis, with a median survival of 3.5 months.

Pantuck et al evaluated the clinical outcome of 236 patients with metastatic RCC (pN0M1) vs that of 86 patients with metastatic RCC and lymph node metastasis (pN1M1). Both groups underwent cytoreductive nephrectomy. The group without lymphadenopathy was noted to have a markedly better survival, with a median of 20.4 months vs 10.5 months for those with pN1M1. Survival benefit improved further to a median of 28 months in those with pN0M1 treated with adjuvant immunotherapy (interferon alfa) vs no demonstrated benefit of adjuvant therapy in patients with pN1M1. In patients with clinically node-negative disease, regional lymphadenectomy did not appear to improve patient outcome, whereas in patients with preoperative lymphadenopathy, regional lymphadenectomy appeared to offer a slight survival benefit as well as a potentially improved response to adjuvant immunotherapy. However, those with both lymph node and systemic metastases had a worse prognosis than all other subgroups.

A more contemporary study from the M.D. Anderson Cancer Center assessed the disease-specific outcome of 40 patients with RCC and nodal metastasis in the absence of other sites of disease. These patients received cytoreductive nephrectomy and extended retroperitoneal lymphadenectomy. Extracranial extension was present in 70% of cases, with 70% recurring at a median of 4.9 months. Overall, 30% of patients had no evidence of disease at a median follow-up of 17.7 months, with the remaining patients deceased (62%) or alive with disease (8%). On multivariate analysis, the presence of >1 positive lymph node (pN2) was predictive of worse recurrence-free survival (hazard ratio of 2.83) and worse overall survival (hazard ratio of 9.33).

On multivariate analysis, pathologic nodal stage (pN2 vs pN1) and tumor Fuhrman grade were predictive of time to recurrence (P = .059 and .023, respectively). Again, these experiences in terms of the prognostic benefit of regional lymphadenectomy at the time of radical nephrectomy preceded the current targeted therapy era. These studies need validation in a more contemporary series treated in the context of these agents.

Most urologic oncologists would advocate the role of performing a regional lymphadenectomy in the presence of preoperative lymphadenopathy in an attempt to render the patient radiographically disease-free (P0) and candidates for adjuvant therapeutic trials. Such an approach should be considered the standard provided the extent and anatomical distribution of the lymphadenopathy is deemed resectable with acceptable expected perioperative morbidity. However, the therapeutic benefit to lymphadenectomy has not been observed in some subsequent reports.

**Obesity**

Obesity affects the therapeutic index of any major abdominal surgery. Among patients undergoing surgery with curative intent, a better prognosis was observed in obese (body mass index > 30 kg/m²) RCC patients. Haferkamp et al identified only a favorable trend, although the underweight patients (body mass index < 18 kg/m²) had a worse prognosis. In both studies, however, obesity was identified as a potential contributor to perioperative morbidity. Nevertheless, it does not appear to be a specific adverse indicator such that deferral of nephrectomy should be considered on the basis of this variable alone in patients without metastatic disease. Obesity in itself should not impact the decision to undergo upfront nephrectomy, although it may make the surgery a more technically challenging procedure. No data are available that directly relates obesity to timing of cytoreductive nephrectomy.

**Reduction of Fractional Percent Tumor Volume**

Nephrectomy is presumed to be of greatest benefit in the absence of metastatic disease and to be of little or no benefit in patients exhibiting much worse clinical features than those of the patient population included in the SWOG and EORTC trials. Incident “metastatic RCC” patients comprise a heterogeneous group with variable extent of metastatic disease, and therefore the extent of benefit from cytoreductive nephrectomy will vary individually. At one end of the spectrum, patients with small-volume metastatic disease, such as an isolated lung lesion, may benefit most from cytoreductive nephrectomy as the primary treatment modality since their features are closest to the curative-intent situation. This concept is called the fractional percent tumor volume (FPTV).
Collins et al.27 from Columbia University reported on 93 patients who had undergone cytoreductive nephrectomy in the context of metastatic disease. Using a cut-point of 90% debulking, the median disease-specific survival differed sharply (median of 18.8 vs 3.6 months; hazard ratio of 5.73; \( P < .001 \) for both). Interestingly, the median tumor size in the high FPTV group was larger (median of 10.6 vs 7.2 cm), which is consistent with a description of “metastasis at small primary size” as a marker of biologically aggressive disease. Among the 77 patients, 64 were in the > 90% removed group.

In a database of more recent cases, Barbatafano et al.28 reported on the Cleveland Clinic experience, relating FPTV vs overall survival in the setting of “nephrectomy followed by VEGF drug.” In this more recent observational cohort (2005–2008), 95% of 75 patients had clear cell histology tumors. On multivariate analysis, FPTV removed and the interval from diagnosis to treatment were independent predictors of PFS. They concluded that in the patients treated with tyrosine kinase inhibitors (TKIs), a high percentage of tumor burden removed was associated with improved PFS. This conclusion does not reach the level of a causative association because high percentage removal often occurs only in the context of relatively low metastatic bulk, ie, an intrinsic disease-biology characteristic reflecting the aggressiveness and resectability of the disease rather than a consequence of treatment decisions.

If the balance of the bulk of metastatic disease that would remain after surgery is significant with only a small burden of the disease resected, then the incremental benefit of surgery will be small to nonexistent.

**Considerations for Nephrectomy in the Era of New Drug Development**

Specific considerations pertain to cytoreductive nephrectomy in contemporary systemic therapy trials. The frequent treatment design in these studies is to use upfront cytoreductive nephrectomy delineating a stark limitation of a strictly empiric treatment algorithm for this patient population.

An individualized treatment plan requires the identification of clear and realistic expectations of therapeutic goals: relief from symptoms, delay of metastatic progression, improved overall survival, minimal exposure to treatment-related risks, and reduced short-term and long-term side effects. These differ from the goals in drug development, which may be defined more narrowly. An emphasis is on side-effect profiles in phase I trials, typically in pretreated but fit patients, whereas in phase II trials, the emphasis is on radiologic response (frequently using RECIST criteria) and PFS, sometimes without a focus on the questions of quality of life and symptomatic control.

In contrast, phase III clinical trials concentrate on overall survival and PFS. In the interest of minimizing heterogeneity within the treatment arms — to limit the number of subjects needed to treat as well as to isolate conceptually the intervention being tested — the patient population being evaluated may represent only a subset of the metastatic RCC patient population that is typically seen in daily clinical practice. Key differences include patient age at presentation, comorbidities, organ reserve, rate of tumor growth, prior treatment, and willingness to travel for therapy. Performance status of the incident population will be more heterogeneous than the on-study population. Most distinct from medical practice directed at an individual, these pivotal clinical trials address the medical treatment in isolation of the nephrectomy decision. The optimal way to combine and sequence these isolated interventions, particularly with regard to medical vs surgical intervention, remains a treatment concept that has not been addressed empirically. Hence, clinicians are faced with the treatment dilemma on how best to proceed to recommending initial cytoreductive nephrectomy or initial medical therapy.

Much of the experience with inpatient, high-dose IL-2 is concentrated in patients with prior nephrectomy. Those who have been treated with IL-2 in prior clinical trials serve as the basis for our “relative optimism” of the potential curative-intent of this systemic approach. Selection of the optimal group for whom to offer this approach — and sometimes obviate all future cancer treatment — remains a significant therapeutic challenge.

In addition, the list of medical interventions with high-quality, phase III randomized data is growing. Among the drugs specifically active on the VEGF pathway, the first oral agent approved by the US Food and Drug Administration was sorafenib, as a result of the TARGET pivotal trial. In this study, patients had received prior therapy, predominantly immunotherapy (82%), and most of them had undergone prior cytoreductive nephrectomy (94%).15 Typical of most second-line therapy clinical trials, subtle differences were noted in terms of performance status and the pattern and rate of tumor growth compared with first-line therapeutic interventions. The European arm of the expanded access program opened after the PFS benefit was reported. The rate of stable disease was reported and stratified by nephrectomy status. As in the pivotal trial, the study population predominantly consisted of patients having previously undergone cytoreductive nephrectomy (929 of 1,031 patients, 90%). The extent of the treatment response appeared similar, with a median PFS of 7.0 months (95% confidence interval [CI], 6.3–7.8) in the nephrectomy population vs a median PFS of 5.2 months (95% CI, 4.0–7.1) in the subgroup of patients with the primary tumor remaining in place.29 The North American expanded access program was also reported.30

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In the setting of planned nephrectomy, a reported single-arm study of 25 metastatic RCC patients receiving between 4 to 8 weeks of sorafenib followed by cytoreductive nephrectomy demonstrated the general feasibility and safety of this neoadjuvant sequence paradigm. However, 1 patient progressed and 1 had a perioperative myocardial infarction. In terms of tumor response, there was a median of 13% (range, 0% to 40%) reduction of the primary tumor size, and 63% of patients had at least 50% necrosis in the primary with neoadjuvant sorafenib. Fig 1 illustrates the objective response of a primary tumor to preoperative sorafenib.

In the sunitinib pivotal trial, 89% of the 375 patients in the sunitinib treatment arm had previously undergone a nephrectomy. The sunitinib expanded access program describes a similar proportion of post-nephrectomy patients (88% among 3,997 patients). The anatomic pattern of spread was similar between those having undergone prior nephrectomy and those with the primary tumor remaining in situ, with some differences in performance status (≥ 2 ECOG): 12% for those who underwent nephrectomy vs 22% for those who did not undergo nephrectomy. A more pronounced difference was seen in those having undergone prior cytoreductive nephrectomy (compared with those with no prior surgery) when treated with immunotherapy (74% and 53%, respectively). Major response was seen in 16% and 9%, respectively; major response is defined as complete and partial responses, but complete responses are infrequent. Finally, the median PFS was comparable but again slightly favored the nephrectomy group, 9.8 vs 8.0 months. Fig 2 illustrates a patient with metastatic RCC, with multiyear stabilization of intrarenal disease on sunitinib therapy.

Currently, two mTOR inhibitors have been studied and tested in phase III kidney cancer trials. In the temsirolimus pivotal trial, the proportion of patients with the primary tumor remaining in situ was significant. At the study initiation, 33% had not previously undergone cytoreductive nephrectomy (68 of 207 in the interferon arm and 70 of 209 in the temsirolimus arm). Other differences in the patient characteristics (in contrast to the sorafenib and sunitinib trials) included a concentration of poor-risk patients (74%), with the remaining 26% being intermediate-risk, using the clinical criteria from the Memorial Sloan-Kettering Cancer Center (MSKCC). Logan et al conducted a subset analysis for the upfront nephrectomy vs nonnephrectomy groups, with the hazard ratio slightly favoring the nephrectomy arm (temsirolimus fared better). However, there was no difference in PFS (P = .47) or overall survival (P = .20). The frequency of a reduction in size (no threshold specified) of the primary tumor in the temsirolimus-treated patients appeared relatively high (37 of 64 patients, 58%), and this was higher than what was observed in the interferon control arm (18 of 59 patients, 31%). The absence of growth is not surprising in our experience, insofar as the growth rate of the primary tumor

Fig 1. — Significant regression of the primary tumor within 3 months of sorafenib therapy. At nephrectomy, the specimen showed clear cell histology.
is often slow compared to that of metastatic sites. On the other hand, this primary tumor stabilization (termed the “stabilization response”) frequency is higher than the overall treatment response (8.6% temsirolimus, 4.8% interferon) or disease stability frequency (32.1% temsirolimus, 15.5% interferon) for the overall disease burden.15 This description of higher frequency of primary tumor stabilization underscores the assertion that targeted drug therapy may be particularly efficacious in the setting where control of the disease at the primary site is an important clinical endpoint.

In the everolimus pivotal trial, patients with metastatic disease limited to those with clear cell histology, prior sorafenib or sunitinib treatment, and progression of disease within 6 months of prior therapy were eligible and accrued to this study.17 Of the 410 patients, 96% (272 in the everolimus arm) had prior nephrectomy, and there was a distribution of posttreatment patients with low (29%), intermediate (56%), and poor (15%) MSKCC risk groups. A higher frequency of disease stabilization (63% everolimus, 32% control arm [placebo]) was noted in terms of overall disease status compared with a cohort of patients in the temsirolimus pivotal trial. There was no separate assessment of the primary tumor response in the few patients in the study with the primary tumor remaining in situ.

Two recent bevacizumab trials were recently completed and reported by the EORTC18 and the Cancer and Leukemia Group B (CALGB).19 The risk category classifications of the treated patients were low (28%), intermediate (56%), and poor (8%) in the EORTC trial, which was similar (26%, 64%, and 10%, respectively) to the CALGB trial. However, primary tumor resection was required in the EORTC trial, whereas in the CALGB trial, 85% of patients had undergone prior cytoreductive nephrectomy. In the CALGB report, nephrectomy status was included in a multivariable proportional hazards model but was determined not to be a predictor of outcome \( (P = .329)\). A separate analysis of rate of primary tumor stabilization was not reported. Similarly, in a randomized trial20 reported in June 2009 studying the new VEGF inhibitor pazopanib, cytoreductive nephrectomy was a study inclusion criteria; hence, no empiric conclusions can be made about its efficacy in patients with the primary tumor in situ.

Overall, these drug trials represent clinical data applicable only to postnephrectomy patient populations. Although not designed to address this specific question, some comparisons have been made to patient populations with the primary tumor in place. Nevertheless, this does not directly address the clinical question of the merits of subsequent cytoreductive nephrectomy in this study cohort as, undoubtedly, subsequent surgical resection was an infrequent treatment intervention.

The feasibility of surgical management in the context of these novel systemic agents appears essentially unchanged. As was concisely stated in a recent editorial,32 major advances in the management of metastatic RCC using small-molecule TKIs and mTOR inhibitors can serve as a “litmus test” of which patients may render a benefit from an aggressive multimodal therapeutic approach.

Margulis et al33 evaluated surgical parameters and perioperative complications in 44 patients treated with targeted molecular therapies before cytoreductive

![Multiyear stability of multiple masses with a solitary kidney of a 26-year-old patient with prior curative intent nephrectomy for RCC, resected metastatic disease (solitary retroperitoneal lymph node at age 49 years), and additional medical therapy, including > 42 months of continuous sunitinib therapy. Tumor dimensions as noted by yellow bars (counterclockwise) were 4.55, 2.40, 5.63, and 4.04 cm in July 2005 and then 2.62, 1.75, 4.46, and 2.41 cm in May 2009.](image-url)
nephrectomy or resection of local renal cell carcinoma recurrence and in 58 patients who underwent up-front surgery. A total of 39 complications occurred in 17 (39%) of the 44 patients treated with preoperative targeted molecular therapy and in 16 (28%) of the 58 patients who underwent up-front resection. The duration, specific type, and time interval from targeted therapy to surgery were not associated with the risk of perioperative morbidity. The authors concluded that preoperative targeted therapy does not appear to increase surgical morbidity among patients subsequently undergoing cytoreductive nephrectomy.

**Development of a Practical Algorithm**

As previously discussed, cytoreductive nephrectomy has a well-established role in the management of RCC due in large part to two surgical series reported by the SWOG and the EORTC. The combined analysis of these series demonstrated a survival benefit to cytoreductive nephrectomy of 5.8 months (vs the median in the group receiving interferon alfa alone). Surgical or medical oncologists must weigh factors such as patient performance status, the expected perioperative morbidity of surgery, and the burden of disease when selecting patients best suited for upfront cytoreductive nephrectomy, similar to selecting patients who will ultimately undergo any form of surgical intervention. We anticipate that these factors will continue to be relevant in an era of targeted drug therapy.

The actual time window during which cytoreductive nephrectomy may improve survival is unclear for an individual patient’s case since the prior randomized studies applied to a dichotomous treatment algorithm consisting of either upfront nephrectomy vs no prior nephrectomy. The overall median survival, even in the nephrectomy arm, was also shorter than that seen in the VEGF-drug pivotal trial treatment groups (utilizing sorafenib, sunitinib, bevacizumab, or pazopanib), even in the control arms. This “now or never” approach to the nephrectomy question was framed in this pivotal experience. Contrasting, a contemporary question can be posed with three time segments: (1) an upfront cytoreductive nephrectomy, (2) a short delay to nephrectomy, on the order of months, that may incorporate a therapeutic trial of targeted medical therapy, or (3) a permanent deferral of surgery. The answer to this question is dependent on the defined patient subsets; this in itself depends on tumor histology, anatomy, and pathologic criteria.

**Good Surgical Candidates With Good Prognostic Features**

The group most suited for upfront surgery consists of those in whom the extent of distant disease is minimal to small and is not associated with adverse biologic features. In some cases, medical therapy can be deferred in those patients unless there is radiographic progression of disease. This subset also can be expected to have the predominance of cases with curative intent; hence, high-dose IL-2 therapy can be considered in this clinical context, although responses to IL-2 therapy can be seen in both low and high metastatic disease-burden situations.

It is unknown if targeted drug therapy would obviate the need for surgery altogether in this subset. Conversely, after high-percentage debulking, some patients may be good candidates for observational approaches without immediate targeted drug therapy following cytoreductive nephrectomy. However, in the context of demonstrated survival benefits of surgery, deferral of systemic therapy in this subset must be considered as temporary, subject to stringent regular metastatic reassessment despite the fact that the optimal surveillance interval is not yet defined.

**Good Surgical Candidates With Some Ambiguous Features**

The middle group represents a unique patient population for therapeutic trials consisting of targeted therapy prior to surgery, which could offer several advantages.

First, identification of patients with TKI-refractory disease, in which the metastatic bulk predominates, is one step. Logically, this is a subset of patients for whom intervention on the asymptomatic primary tumor would offer no advantage for immediate symptom control. Accrued experience with upfront sunitinib and second-line sorafenib trials has shown that this likely represents less than a quarter of unselected cases, ie, those with primary tumor progression during treatment with these agents. Hence, this drug-response criterion may be in part a surrogate marker for the identification of tumors that are not of clear cell histology, as radiologic response rates with VEGF-directed therapy are superior for clear cell RCC vs other histology.

Second, patients exhibiting an excellent response of metastatic sites to targeted therapy, but with a minimal response of the primary tumor, are ideally suited for subsequent surgical intervention. The FPTV to be removed would be more beneficial at the later time point than before the targeted therapy. It is currently unclear what the relative frequency of this “mixed treatment response” is in which the primary becomes more dominant even as the metastases regress.

Third, occasionally the size decrease of the primary tumor can at least render a nephron-sparing approach into a feasible consideration (partial nephrectomy instead of radical nephrectomy) without compromising treatment-specific outcomes.

**Marginal Surgical Candidates**

Finally, for some patients, upfront surgery appears to be only marginally feasible. In this case, consideration of neoadjuvant (or “first”) therapy may be made independently of potential PFS or overall survival benefits.
Neoadjuvant therapy in the setting of unresectable localized RCC, or in the setting of metastatic RCC with borderline features, may serve as a means to select those who may have a durable response with a multimodal approach. Furthermore, this sequence strategy exhibits a lower short-term risk compared to potentially morbid surgery of questionable benefit.32

In other situations in which the patient is a marginal surgical candidate (eg, in the context of significant preoperative comorbidities), aggressive surgical intervention may not be deemed feasible. Thus, systemic therapy with a primary endpoint to provide symptom control and stability of disease (with the survival benefit being questionable in this context) seems reasonable, particularly in patients seeking some form of therapy. Again, frequent serial radiographic and laboratory re-evaluation is essential in order to reassess the balance between tumor response and patient-specific comorbidities.

Discussion
The art of medicine demands a synthesis of currently available scientific literature, principles of tumor biology, and clinical experience. Natural history dominates prognostic recommendations for most RCC patients, but this should not lead to nihilism about the treatment choice process. The significant impact that can be achieved with aggressive multimodal therapy for this patient population is rewarding and serves as the platform for future studies into the pathogenesis of RCC. By their nature and design, initial pivotal trials emphasize isolated treatment and, although not ideal for making definitive conclusions, one should not despair from synthesizing the combined results of these studies.

A multidisciplinary approach to locally advanced or metastatic RCC that integrates targeted therapy (in single or multiagent regimens) with aggressive surgical consolidation should be considered the standard treatment paradigm at this time. Each patient’s treatment recommendations must be made on an individual basis, taking into account the burden of metastatic disease (bulk, single vs multiple sites, and specific sites of disease), patient-specific considerations (performance status, clinical features, patient treatment preferences, and risk stratification category), as well as physician experience and available resources. General prognostic scoring systems and models can define the patient subset for which the convalescence is relatively shorter than the anticipated overall survival increment.

General prognostic scoring systems have been validated as an essential clinical consideration for stage IV metastatic RCC patients in terms of treatment options or patient populations best suited for clinical trials. The published literature on targeted drug therapy in the context of metastatic RCC is dominated by the sequence of cytoreductive nephrectomy followed by targeted drug therapy. The IL-2 clinical studies, including the important albeit infrequent (but durable) complete responses, also have focused on the postnephrectomy patient population. There is some limited literature on targeted drug therapy among patients with the primary tumor in situ. This clinical experience has validated the feasibility of upfront targeted therapy followed by debulking cytoreductive nephrectomy. Initial targeted therapy with the diseased kidney remaining in place appears feasible in most series emphasizing therapy in patients who would not be deemed surgical candidates. Other data (P.E.S., unpublished data) with surgery on metastatic RCC patients following targeted therapy has demonstrated that the degree of scarring and inflammation can vary dramatically. Nevertheless, in most cases, cytoreductive nephrectomy can be performed safely and effectively with limited or no morbidity. A direct relationship between operability and survival benefit is not guaranteed, even in apparently surgically feasible cases.

The availability of medical therapy associated with a survival impact should influence our treatment approach to the individual patient from the conventional “black or white” philosophy on the merit of surgical resection to rather shades of gray, where the potential benefits and drawbacks of surgical intervention must be weighed. While this type of treatment decision is not validated prospectively, it is best suited for intermediate-risk metastatic RCC patients. Whether a neoadjuvant or adjuvant therapy approach should be offered and recommended is an important contemporary area of debate. However, for patients with metastatic disease that is more bulky, multifocal, or otherwise advanced, neoadjuvant therapy is a key consideration in order to determine if the systemic disease can be stabilized with systemic therapy before aggressive surgical consolidation is recommended.

Although not discussed here, routine practice should also consider the strategic use of locally directed therapy of metastases that encompasses radiotherapy and metastatectomy surgery. For some cases, this emphasis can be a valuable and well-tolerated option in place of VEGF or mTOR medical therapy.

Adjuvant testing is already underway as randomized trials, such as the Eastern Cooperative Oncology Group E2805 ASSURE trial. This may partially address the clinical question of the merit of neoadjuvant therapy in minimizing the risk of metastatic progression. If visible metastasis progression is retarded in those with no evident disease (including some with minute but not obvious disease), it may help when the metastasis is actually visible but still small. Nevertheless, the results of this study and similar ones are not anticipated for years. Ideally, the merits of upfront vs delayed or permanently deferred nephrectomy in metastatic disease in clinically or pathologically defined subsets of patients on targeted drug therapy is a question that merits prospective, randomized-testing.
Conclusions
Empiric data addressing the sequencing question of cytoreductive nephrectomy and newer drug therapies are currently lacking. The growing body of experience in not only selecting the cases best suited for nephrectomy, but also understanding the predictors of disease progression and treatment response may strongly influence our decision process. The criteria for defining the “well-selected” surgical candidate will continue to evolve, and the issue of optimal timing may as well. The rapidly expanding application of new drugs and their potential combinations will likely add to the therapeutic armamentarium. The optimal integration of surgery and systemic agents will be an area of continued debate and development.

References