Original Article

Role of Surgery for Locally Advanced and Metastatic Renal Cell Carcinoma

Robert Torrey, MD[a]; Philippe E. Spiess, MD[b]; Sumanta K. Pal, MD[c]; and David Josephson, MD[a]; *Duarte, California, and Tampa, Florida*

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Abstract
Both locally advanced and metastatic renal cell carcinoma (RCC) present a challenge in terms of their optimal management. This article reviews the literature and evaluates the role of surgery in the treatment of advanced RCC. Surgery is the optimal treatment for locally advanced RCC and minimal, resectable, metastatic disease. Patients with metastatic disease, and some forms of locally advanced disease, may also benefit from multimodal management with local surgical therapy and systemic treatment using either immunotherapy or targeted therapy. Regardless of the disease stage, patients with locally advanced or metastatic RCC represent heterogenous patient populations with different disease characteristics and risk factors. Individualization of care in the setting of a sound oncologic framework may optimize the risk/benefit ratio within individual patient cohorts. (*JNCCN* 2011;9:985–993)

Historically, renal cell carcinoma (RCC) has been a formidable cancer with limited responses to both radiation and systemic management. Currently, surgery offers the only real chance of cure for patients with cancer localized to the kidney and retroperitoneum, and occasionally to those with limited metastatic disease. However, significant strides toward improved systemic treatments have been made. Although many of these approaches are not curative for patients with metastatic disease, they have been associated with improved oncologic outcomes, and further study may show that they improve the therapeutic outcomes for patients with locally advanced disease when given in the adjuvant setting. Multimodal treatment, incorporating both local and systemic therapy, is gradually becoming a standard approach for the treatment of advanced disease. This article describes the current role of surgery in the management of locally advanced and metastatic RCC and considers some of the systemic treatment options that may be used in a multimodal setting.

From the [a]Division of Urology/Urologic Oncology, City of Hope Cancer Center, Duarte, California; [b]Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, Florida; and [c]Department of Medical Oncology and Experimental Therapeutics, City of Hope Cancer Center, Duarte, California.

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Correspondence: David Josephson, MD, Tower Urology at Cedars-Sinai Office Towers, 8635 W. 3rd Street, Suite 1 West, Los Angeles, CA 90048. E-mail: josephsond@towerurology.com

Locally Advanced RCC

Locally advanced RCC affects a diverse group of patients, including those with venous thrombus, venous invasion, adrenal involvement, invasion through the capsule into surrounding fat, and invasion into surrounding visceral structures. Surgical management of these patients requires an aggressive approach to achieve locoregional control, with consideration of adjuvant systemic therapy.

Staging Changes

Recently, RCC underwent several AJCC staging modifications[1] as follows: 1) T2 lesions were subclassified to lesions either larger than 7 and up to 10 cm, or greater than 10 cm; 2) adrenal involvement is now T4 if involved through direct extension of the lesion, and M1 if involved through a metastatic process; 3) renal vein involvement is now T3a; and 4) nodal involvement is no longer classified by the number of nodes, but as being present or absent.

Preoperative Details

The preoperative management of patients with locally advanced disease is often difficult because it is hard to clearly identify patients with advanced disease, choose appropriate surgical candidates, and determine prognosis based on preoperative clinical parameters. Multidetector-row CT (MDCT) is currently the ideal imaging modality for diagnosing RCC and evaluating the extent and stage of disease. MDCT has been associated with 91% accuracy for tumor staging and up to 100% accuracy for assessment of venous tumor invasion.[2] With improvements in CT technology, MRI, which had once been the mainstay of venous tumor evaluation, is now used mostly in the setting of unclear studies from the venous and staging standpoint.[3]

The use of prognostic nomograms has also been developed. These combine numerous clinical features, such as anatomic tumor extent, histologic tumor type and grade, evidence of tumor necrosis, presence of symptoms, performance status, and laboratory parameters (e.g., serum lactate dehydrogenase, calcium, hemoglobin, erythrocyte sedimentation rate [ESR]) to give a better prediction of disease outcome. Future nomograms will also likely include molecular markers (expression of hypoxia inducible factors, regulators of cell cycle and apoptosis, cellular adhesion molecules) to improve clinical prognostications.[4,5]

Ipsilateral Adrenalectomy

Patients with RCC and adrenal gland involvement have a worse prognosis than those who have perinephric fat involvement, thus contributing to the recent AJCC staging changes.[1,6–8] O'Malley et al.[9] reviewed some of the larger series examining the capabilities of cross-sectional imaging (CT/MRI) in the preoperative detection of adrenal gland involvement. Although the positive predictive value was found to range between 26% and 93%, most values were 50% or less. Conversely, the negative predictive value was found to range between 96% and 100%, indicating that CT/MRI is helpful when no adrenal involvement is suspected, but not as helpful when involvement is suspected.[9]

Solitary, synchronous, ipsilateral adrenal involvement has an incidence of 1% to 5%.[9] Comparatively, Siemer et al.[10] documents a 5.5% adrenal gland involvement with a 1.8% incidence of solitary, synchronous, ipsilateral adrenal metastasis without lymph node involvement or distant metastasis when adrenalectomy is performed. Adrenalectomy would likely only benefit the approximately 2% of patients with solitary, synchronous, ipsilateral adrenal involvement, because the others have either no involvement or metastatic disease.[9,10] Although adrenalectomy has been shown not to increase the complication rate,[10] a theoretical risk of adrenal insufficiency is present. Yokoyama and Tanaka[11] showed that the reserve of adrenocortical function was impaired 2 weeks after surgery. Ipsilateral adrenalectomy at the time of radical nephrectomy, as described by Robson et al.,[12] should likely be limited to those with suspicious findings on imaging or those with suspicious operative findings, unless surgically unavoidable. Furthermore, patients with metastatic disease to distant sites or lymph nodes will likely not benefit from ipsilateral adrenalectomy, and this can be avoided unless surgically indicated.[9]

Capsular Invasion With No Perinephric Fat Invasion

The incidence of capsular invasion is approximately 22%.[13] Although some debate exists regarding the implications of capsular invasion, studies have shown it to be associated with a higher grade and larger tumor size. Multivariate analysis has shown capsular involvement to be an independent prognostic factor of recurrence-free survival, and studies have shown that patients with stage I to II tumors who had capsular involvement had the same recurrence-free survival as those with perinephric tissue invasion (pT3N0M0).[13] Moreover, patients with stage pT2 RCC and capsular invasion had significantly worse 5-year disease-specific survival compared with those with pT2 disease who did not have any capsular invasion.[14]

Perinephric Fat or Renal Sinus Fat Invasion

Perinephric fat and renal sinus fat invasion are both concerning pathologic findings and have implications for treatment. A retrospective review of 1087 patients found that 17% had perinephric fat or renal sinus fat invasion, with a 5-year cancer-specific survival rate of 36%.[6] A Korean study also showed that patients with perinephric fat infiltration had significantly worse 5-year cancer-specific and disease-free survivals compared with those with RCC contained in the kidney (pT1/pT2). However, most of the effects were seen in those with lesions larger than 7 cm, because those with lesions 7 cm or less had cancer-specific and disease-free survivals similar to those

with pT2 RCC. Furthermore, recurrence occurred in 44% of patients with lesions larger than 7 cm compared with only 15% in patients with lesions 7 cm or less.[15]

Perinephric fat invasion and renal sinus fat invasion both represent pT3a disease, but questions have arisen as to whether these are truly equivalent. One study showed no significant difference in cancer-specific or disease-free survivals between renal sinus fat invasion and perinephric fat invasion.[15] However, a study from the Mayo Clinic showed that renal sinus fat invasion is a more ominous finding, wherein patients were 63% more likely to die of RCC than patients with perinephric fat invasion, and the risk remained statistically significant on multivariate analysis. The 5-year cancer-specific survival rate was 51% for patients with perinephric fat invasion, compared with 26% for patients with renal sinus fat invasion.[16] The Mayo Clinic also assessed a group of 33 patients with pT1 RCC who subsequently died of their disease. After their death, a pathologist resectioned their preserved specimens and showed that 42% of the patients had previously unrecognized renal sinus fat invasion compared with only 6% in a control group of 33 patients with RCC who did not die of their disease. Furthermore, 67% of the patients with RCC who died had renal sinus fat involvement or renal sinus small vein invasion, compared with only 21% in the control group.[17]

In summary, if oncologic surgical principles are adhered to, then invasion of the capsule, perinephric fat, or renal sinus fat is unlikely to affect the technique or method of operation. However, this information is important to review postoperatively because it may better identify patients with aggressive pathologic features potentially suitable for adjuvant therapy clinical trials.

The Role of Lymphadenectomy

The prevalence of positive nodes at the time of radical nephrectomy has been shown to range between 3% and 64%, with a median of 14% and a highest incidence of 64% reported within an autopsy series.[18] In 2009, the EORTC Genitourinary Group released the results of the first randomized trial comparing lymph node dissection at the time of radical nephrectomy and radical nephrectomy alone in patients with clinical N0M0 disease. They found that of the patients who underwent lymph node dissection, 4% had positive nodes on final pathologic evaluation. Palpably suspicious nodes at the time of surgery yielded a 20% positivity rate compared with 1% if nodes were not suspicious on examination. For patients who did not undergo a regional lymph node dissection, nodes were biopsied or selectively removed if they were suspicious on palpation. Suspicious nodes in this patient group were positive 12% of the time. Although the complication rate did not differ significantly between the groups, the study also showed no significant differences in overall survival, time to progression of disease, or progression-free survival.[19] However, this study examined predominantly low-risk patients with low stage and low disease grade, and an overall smaller proportion of patients with lymph node involvement compared with the typical population of patients with RCC. The implications of these findings compared with a high-risk group with potential locally advanced disease remains unclear.[20]

The role of lymphadenectomy and the ideal template of dissection in RCC are also unresolved because different templates of discussion show different node positivity rates depending on their surgical extent. Terrone et al.[21] found that the incidence rate of positive lymph nodes was significantly higher when 13 or more nodes were removed (20.8% vs. 10.2% for < 13 nodes; $P < .001$). Unfortunately, preoperative imaging and intraoperative examination are not accurate in detecting evidence of lymph node involvement. Two surgical series have shown that when preoperative imaging or intraoperative examination showed enlarged lymph nodes, pathologic disease was actually present in only 31% to 42% of cases.[22,23] Furthermore, in a study by Studer and Birkhauser,[20] the false-positive nodes were enlarged because of inflammatory changes (especially in the presence of necrosis) or follicular hyperplasia.[23] Conversely, nodes that appeared negative on preoperative imaging or during intraoperative examination have been described as positive with micrometastatic disease in 2% to 6% of cases, [19,22,24] and patients with isolated lymph node metastases (with or without preoperative enlarged lymph nodes) and no other metastasis have been described in between 4% to 7% of cases.[25,26] These patients would potentially benefit from lymph node dissection as long as the disease was confined to these nodes. In patients with more pathologically advanced disease (pTxN1–2M0), 83% of patients had clinical evidence of nodal involvement preop-

eratively and the remainder had suspicious nodes, noted intraoperatively. Interestingly, 30% of the patients had no evidence of disease at a median follow-up of 17.7 months.[27] These results were similar to what was found by Karakiewicz et al.[26] with a 31% 10-year actuarial disease-specific survival and a 28% 15-year actuarial disease-specific survival in patients with TanyN1–2M0 disease, indicating that approximately 30% of patients will have prolonged survival if isolated metastatic lymph nodes are removed. Pantuck et al.[25] retrospectively reviewed 1087 patients and found that in node-negative patients, a lymph node dissection could be performed with no increase in morbidity, but it offered no survival benefit to patients. Conversely, in patients with positive nodes, a lymph node dissection could be performed safely with an improved survival and a trend toward an improved response to immunotherapy.

In summary, although no level 1 data indicate the therapeutic benefit of a lymph node dissection, associated morbidity tends to be limited, and because preoperative and intraoperative examination of nodes is imprecise, a reasonable approach would be to perform a limited regional node dissection in patients with a lower suspicion of lymphatic involvement, and a more extensive node dissection in those with more adverse clinical/pathologic features. This practice can only improve the accuracy of the surgical staging for these patients and, with new medications being approved rapidly for metastatic disease, these patients may gain benefit from adjuvant therapy.

Venous Thrombus and Venous Invasion

RCC that involves the venous system is a complex clinical scenario, with one study showing an overall incidence of 19%.[28] Most patients had disease confined to the renal vein, whereas extension into the inferior vena cava occurred in 7% and extension above the diaphragm was relatively rare, with a reported incidence of 1%.[28] The precise staging of venous tumors has been complicated because variances are present in the previous scientific literature. However, data suggest that although no difference is seen in reported oncologic outcomes based on the level of vena caval thrombus, a favorable difference is seen when comparing isolated renal vein involvement and vena cava involvement of any level.[29,30] Moreover, regardless of its independent prognostic ability, venous involvement has been associated with more aggressive tumors.[31]

Various staging systems have been developed to describe the level of tumor thrombus within the venous system. Simpler staging systems, such as the TNM classification, describe thrombus as above or below the diaphragm,[1] whereas other systems, such as the one proposed by Neves and Zincke,[32] base staging on more complex anatomic details.

Operative techniques to manage these tumors have improved over time, but the procedure remains complicated and arduous. Before the work of Robson, tumor thrombectomy was considered a futile operation.[33] In the 1970s, it became a more mainstream operation at specialized centers, and over time advancements with cardiopulmonary bypass, deep hypothermic circulatory arrest, venovenous bypass, liver transplantation techniques, and inferior vena cava (IVC) reconstruction techniques have allowed for greater operative success.[33–36]

Preoperative imaging has similarly improved with current thin-cut MDCT using multiplanar reconstruction capabilities demonstrating equivalent competency in diagnosing the presence or absence and extent of tumor thrombi when compared to MRI.[36–38] MDCT may be preferably used as an initial study with potential subsequent MRI use in equivocal cases. Furthermore, MRI may be superior in the evaluation for vena cava wall invasion or in evaluating the relationship between the thrombus and the hepatic veins.[36] Intraoperative imaging is also being used in the form of transesophageal echocardiography, which has been shown to help identify loose tumor thrombus migration into the right atrium and air embolisms, both of which can be dealt with intraoperatively, thereby preventing potentially catastrophic complications.[39]

Patients with nonmetastatic disease are most likely to benefit from surgery. The 5-year disease-specific survival for patients with nonmetastatic disease is 40% to 65% compared with only 7% to 28% for patients with metastatic disease. However, even in the metastatic setting, cytoreductive nephrectomy with tumor thrombectomy, when combined with immunotherapy, has been shown to improve survival compared with either no treatment, surgery alone, or immunotherapy alone.[40]

Invasion into the venous wall is problematic from both an oncologic and surgical standpoint. Ciancio and Soloway[41] described 3 patients of 60 who required resection of the IVC during surgery. In 2 of the pa-

tients (3%), this was because of venous wall invasion. Fortunately, in patients with complete obstruction to the venous channel, the IVC can be resected without replacement because of the development of collateral venous channels. If patients have not developed collateral venous channels, then reconstruction of the IVC with autologous or prosthetic graft material should be strongly considered, because patients who do not undergo this procedure will be more prone to the development of severe lower extremity edema.[41,42]

In summary, these tumors require proper preoperative planning and excellent surgical technique at a facility capable of complex surgical cases, with the understanding that even in the best hands adverse clinical outcomes can occur. However, patients tend to have better oncologic outcomes with surgery, even in appropriately selected patients with minimal metastatic disease.

Treatment of Cancer Invading Adjacent Organs

Pathologic invasion of adjacent organs is an aggressive feature that frequently involves the colon, spleen, pancreas, or diaphragm.[43] Preoperative determination of T4 status is difficult, potentially because of a desmoplastic reaction that frequently occurs around the tumor. One study showed true invasion of adjacent organs in only 40% of cases when patients appeared to have T4 disease preoperatively.[43] Metastatic disease is frequently coexistent, with approximately 1% of patients presenting with isolated adjacent organ invasion and no distant disease.[43] However, in this very small patient population, those with pT4 disease in the absence of regional lymph node or distant metastatic disease had a 42-month survival benefit with surgical resection compared with those not undergoing surgery.[44] In the absence of better preoperative staging tools, it is reasonable to proceed with surgical management in appropriately selected patients with the knowledge that many will be downstaged and that a small portion of patients who do have clinically localized disease with no lymphatic or distant disease will benefit from surgical management.

Neoadjuvant and Adjuvant Therapy

Certain patients will be at risk for tumor recurrence despite good local control of the tumor and an apparent postoperative disease-free status. Adjuvant therapy with radiotherapy, chemotherapy, immunotherapy, and hormonal therapy has not been found to be beneficial in these patients. However, data from patients with metastatic disease undergoing targeted therapy have shown favorable outcomes, which may similarly apply in the adjuvant setting for patients with locally advanced disease. Furthermore, when given in a neoadjuvant setting, case series have shown that targeted therapy downstages previously unresectable renal tumors and lymphadenopathy, and is associated with a small possibility of a decrease in the tumor thrombus level.[45–49]

Unfortunately, targeted therapy may also have negative results, such as side effects and a risk of increased local tumor extent and metastatic progression.[50,51] Therefore, Bex et al.[52] recommended that targeted therapy not be given in the adjuvant setting except in the context of a clinical trial. Randomized trials are therefore necessary to understand the role of neoadjuvant or adjuvant targeted therapy in patients with locally advanced disease.

Surgical Management of Metastatic RCC

In a literature review examining the epidemiologic and socioeconomic burden of metastatic RCC, Gupta et al.[53] defines metastatic RCC as occurring in 25% to 30% of patients at diagnosis, with only 5% having solitary metastasis. Furthermore, survival at 5 or more years ranges from 5% to 10%, with an overall median survival of less than 1 year.[53] Managing patients with metastatic RCC is complicated from a treatment standpoint, because they have historically been mostly resistant to available systemic therapies. Many practitioners now feel that in appropriately selected candidates, the best approach to treating metastatic RCC may be in the form of multimodal therapy—such as the combination of surgery (i.e., cytoreductive nephrectomy, tumor debulking, metastasectomy) and systemic treatment (either immunotherapy or targeted therapy).

Cytoreductive Nephrectomy

In a review by Rini and Campbell,[54] the ideal candidate for cytoreductive nephrectomy is described as a patient who has good performance status, a resectable primary tumor representing most of the tumor burden, no evidence of rapidly progressing extrarenal disease, and no prohibitive medical comorbidities. However, questions still exist as to the exact timing of nephrectomy and how to treat patients who are not ideal candidates.

The mechanism underlying the survival benefit of cytoreductive nephrectomy is not well understood. Theories include reduction of disease burden, microenvironmental changes, improved postoperative immunologic status, and removal of the primary source of growth factors, thereby allowing metastases to regress or stabilize.[54] Regardless of the mechanism, 2 randomized trials have shown the benefit of cytoreductive nephrectomy in the setting of immunologic systemic therapy.[55,56] A combined evaluation of the 2 trials yielded a median survival of 13.6 months (surgery and interferon therapy) versus 7.8 months (interferon therapy alone), with a 31% decrease in the risk of death when surgery was added to interferon therapy.[57] Although no randomized data exist for interleukin-2 (IL-2) therapy in the cytoreductive setting, a group from the University of California, Los Angeles determined that patients receiving IL-2 after cytoreductive nephrectomy had longer survival.[58] More research in this area is needed to determine the ideal form of postoperative immunotherapy, but overall, the use of IL-2 over interferon is favored for patients who are good surgical candidates with a good performance status.

Although high-dose IL-2 results in favorable oncologic outcomes, it has been associated with a significant side effect profile.[59,60] Comparatively, targeted therapy has been associated with increased response rates (mostly partial responses) and improved survival compared with immunotherapy in general, and has also been associated with a more favorable side effect profile.[49,52] Six different targeted therapy medications have been approved by the FDA for the treatment of patients with advanced RCC: sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, and bevacizumab combined with interferon. Unfortunately, no randomized data is available on the combination of cytoreductive surgery and targeted therapy. However, many practitioners have extrapolated the findings of combined surgery and immunotherapy to the targeted therapy population, and therefore those who are candidates for surgery will undergo cytoreductive nephrectomy before targeted systemic therapy.

The heterogenous nature of both the metastatic disease presentation and the underlying health of the patient have led physicians to consider individualized treatment. Patients who are healthy with a good performance status (ECOG performance status < 2), little distant disease, no brain metastasis, and no associated adverse biologic features are excellent candidates for upfront cytoreductive nephrectomy with delayed systemic treatment using either targeted therapy or immunotherapy. Patients who are not good surgical candidates (i.e., those with significant comorbid disease, unresectable localized disease, or metastatic RCC with borderline features) or who have adverse tumor features despite being good surgical candidates (i.e., increased metastatic bulk compared to the primary lesion, or concerns for a non–clear cell type) may benefit from up-front systemic treatment using targeted therapy with close observation. Systemic therapy is the most clinically relevant treatment option for these patients and will likely predict the natural history of the disease. Patients whose disease status improves in response to targeted therapy, and those in whom performance status improves, may be candidates for deferred cytoreductive nephrectomy. Furthermore, patients whose primary lesion decreases may even be candidates for nephron-sparing surgery, particularly if they have a solitary kidney.[61]

Metastasectomy

Although metastatic disease usually occurs in more than one location,[53] metastasectomy is most commonly performed in patients who have a clinical possibility of becoming disease-free after low-volume metastatic resection. Although metastasectomy has been successfully performed in various regions of the body,[62–68] favorable features that are more amenable to resection include solitary lesion (preferably in the lung), curative resection at first metastasis, metachronous presentation, disease-free interval greater than 12 months, and younger age at presentation.[66] One study showed that patients who had a partial response after treatment with IL-2 had better survival if they underwent surgical resection for residual disease compared with patients who had complete or partial responses to IL-2 but no surgery.[67] Kavolius et al.[66] showed that patients undergoing curative metastasectomy had an improved 5-year overall survival compared to those undergoing noncurative resection or no surgery (44% vs. 14% and 11%, respectively), especially in patients with lung-only metastasis (54%). Furthermore, they showed no difference in 5-year overall survival after curative resection of second and third metastases. In a study from MD Anderson Cancer Center, adverse risk factors were described as positive local recur-

rence margin, increased size of recurrence, presence of sarcomatoid features, and abnormal serum alkaline phosphatase or lactate dehydrogenase. Patients with no adverse features had an improved cancer-specific survival of 111 months compared with those with one risk factor (40 months) or those with more than one risk factor (8 months).[69]

In summary, immunotherapy and targeted therapy are systemic options that have opened a gateway for treating patients with metastatic disease; however, several unanswered clinical questions remain regarding the optimal targeted agents or combinations thereof, and the optimal timing of cytoreductive nephrectomy (pre/post targeted therapy). Furthermore, with one study showing improved overall and progression-free survival in patients with metastatic RCC and poor-risk features who received temsirolimus compared with interferon alfa regardless of nephrectomy status, questions exist as to the necessity of nephrectomy in poor-risk patients.[70] Randomized controlled trials are needed to appropriately address these unanswered therapeutic questions.

Palliation

Surgery is one option for the treatment of patients with severe symptoms secondary to advanced RCC, and it has been used for palliation of symptoms from localized and metastatic disease, such as local pain, bony pain, and uncontrolled gross hematuria, and for control of paraneoplastic syndromes. However, less-invasive palliative methods, such as those offered by interventional radiology (i.e., renal embolization), are also effective for symptomatic control, and are in many cases an option for patients who are not good surgical candidates.[59]

Conclusions

Despite advances in treatment approaches, surgery remains the best management option for those with locally advanced RCC and is a beneficial adjunct in the multimodal management of metastatic RCC. Because of the heterogenous nature of patients in both the locally advanced and metastatic populations, individualization of care is most likely the best approach in most cases to ensure a favorable risk/benefit ratio. Further studies are needed to determine the ideal method of combining surgery and systemic therapy in this multimodal approach to patients with locally advanced and metastatic RCC.

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References

1. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. New York, NY: Springer; 2010.
2. Schreyer HH, Uggowitzer MM, Ruppert-Kohlmayr A. Helical CT of the urinary organs. Eur Radiol 2002;12:575–591.
3. Mueller-Lisse UG, Mueller-Lisse UL. Imaging of advanced renal cell carcinoma. World J Urol 2010;28:253–261.
4. Furniss D, Harnden P, Ali N, et al. Prognostic factors for renal cell carcinoma. Cancer Treat Rev 2008;34:407–426.
5. Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. Urol Clin North Am 2008;35:613–625.
6. Han KR, Bui MH, Pantuck AJ, et al. TNM T3a renal cell carcinoma: adrenal gland involvement is not the same as renal fat invasion. J Urol 2003;169:899–903.
7. Thompson RH, Leibovich BC, Cheville JC, et al. Should direct ipsilateral adrenal invasion from renal cell carcinoma be classified as pT3a? J Urol 2005;173:918–921.
8. Ficarra V, Galfano A, Guille F, et al. A new staging system for locally advanced (pT3-4) renal cell carcinoma: a multicenter European study including 2,000 patients. J Urol 2007;178:418–424.
9. O'Malley RL, Godoy G, Kanofsky JA, et al. The necessity of adrenalectomy at the time of radical nephrectomy: a systematic review. J Urol 2009;18:2009–2017.
10. Siemer S, Lehmann J, Kamradt J, et al. Adrenal metastases in 1635 patients with renal cell carcinoma: outcome and indication for adrenalectomy. J Urol 2004;171:2155–2159.
11. Yokoyama H, Tanaka M. Incidence of adrenal involvement and assessing adrenal function in patients with renal cell carcinoma: is ipsilateral adrenalectomy indispensable during radical nephrectomy? BJU Int 2005;95:526–529.
12. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. J Urol 1969;101:297–301.
13. Klatte T, Chung J, Leppert JT, et al. Prognostic relevance of capsular involvement and collecting system invasion in stage I and II renal cell carcinoma. BJU Int 2007;99:821–824.
14. Jeong IG, Jeong CW, Hong SK, et al. Prognostic implication of capsular invasion without perinephric fat infiltration in localized renal cell carcinoma. Urology 2006;67:709–712.
15. Yoo C, Song C, Hong JH, et al. Prognostic significance of perinephric fat infiltration and tumor size in renal cell carcinoma. J Urol 2008;180:486–491.
16. Thompson RH, Leibovich BC, Cheville JC, et al. Is renal sinus fat invasion the same as perinephric fat invasion for pT3a renal cell carcinoma? J Urol 2005;174:1218–1221.
17. Thompson RH, Blute ML, Krambeck AE, et al. Patients with pT1 renal cell carcinoma who die from disease after nephrectomy may have unrecognized renal sinus fat invasion. Am J Surg Pathol 2007;31:1089–1093.
18. Phillips CK, Taneja SS. The role of lymphadenectomy in the surgical management of renal cell carcinoma. Urol Oncol 2004;22:214–223.
19. Blom JH, van Poppel H, Marechal JM, et al. Radical nephrectomy with and without lymph-node dissection: final results of European

Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol 2009;55:28–34.

20. Studer UE, Birkhauser FD. Lymphadenectomy combined with radical nephrectomy: to do or not to do? Eur Urol 2009;55:35–37.
21. Terrone C, Guercio S, De Luca S, et al. The number of lymph nodes examined and staging accuracy in renal cell carcinoma. BJU Int 2003;91:37–40.
22. Phillips E, Messing EM. Role of lymphadenectomy in the treatment of renal cell carcinoma. Urology 1993;41:9–15.
23. Studer UE, Scherz S, Scheidegger J, et al. Enlargement of regional lymph nodes in renal cell carcinoma is often not due to metastases. J Urol 1990;144:243–245.
24. Minervini A, Lilas L, Morelli G, et al. Regional lymph node dissection in the treatment of renal cell carcinoma: is it useful in patients with no suspected adenopathy before or during surgery? BJU Int 2001;88:169–172.
25. Pantuck AJ, Zisman A, Dorey F, et al. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol 2003;169:2076–2083.
26. Karakiewicz PI, Trinh QD, Bhojani N, et al. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease: prognostic indicators of disease-specific survival. Eur Urol 2007;51:1616–1624.
27. Canfield SE, Kamat AM, Sanchez-Ortiz RF, et al. Renal cell carcinoma with nodal metastases in the absence of distant metastatic disease (clinical stage TxN1-2M0): the impact of aggressive surgical resection on patient outcome. J Urol 2006;175:864–869.
28. Blute ML, Leibovich BC, Lohse CM, et al. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int 2004;94:33–41.
29. Wagner B, Patard JJ, Mejean A, et al. Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol 2009;55:452–459.
30. Moinzadeh A, Libertino JA. Prognostic significance of tumor thrombus level in patients with renal cell carcinoma and venous tumor thrombus extension. Is all T3b the same? J Urol 2004;171:598–601.
31. Kim HL, Zisman A, Han KR, et al. Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? J Urol 2004;171:588–591.
32. Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol 1987;59:390–395.
33. Vaidya A, Ciancio G, Soloway M. Surgical techniques for treating a renal neoplasm invading the inferior vena cava. J Urol 2003;169:435–444.
34. Skinner DG, Pritchett TR, Lieskovsky G, et al. Vena caval involvement by renal cell carcinoma. Surgical resection provides meaningful long-term survival. Ann Surg 1989;210:387–392.
35. Ciancio G, Gonzolez J, Shirodkar SP, et al. Liver transplantation techniques for the surgical management of renal cell carcinoma with tumor thrombus in the inferior vena cava: step-by-step description. Eur Urol 2011;59:401–406.
36. Pouliot F, Shuch B, Larochelle JC, et al. Contemporary management of renal tumors with venous tumor thrombus. J Urol;184:833–841.
37. Lawrentschuk N, Gani J, Riordan R, et al. Multidetector computed tomography vs magnetic resonance imaging for defining the upper limit of tumour thrombus in renal cell carcinoma: a study and review. BJU Int 2005;96:291–295.
38. Hallscheidt PJ, Fink C, Haferkamp A, et al. Preoperative staging of renal cell carcinoma with inferior vena cava thrombus using multidetector CT and MRI: prospective study with histopathological correlation. J Comput Assist Tomogr 2005;29:64–68.
39. Sigman DB, Hasnain JU, Del Pizzo JJ, et al. Real-time transesophageal echocardiography for intraoperative surveillance of patients with renal cell carcinoma and vena caval extension undergoing radical nephrectomy. J Urol 1999;161:36–38.
40. Zisman A, Wieder JA, Pantuck AJ, et al. Renal cell carcinoma with tumor thrombus extension: biology, role of nephrectomy and response to immunotherapy. J Urol 2003;169:909–916.
41. Ciancio G, Soloway M. Resection of the abdominal inferior vena cava for complicated renal cell carcinoma with tumour thrombus. BJU Int 2005;96:815–818.
42. Duty B, Daneshmand S. Resection of the inferior vena cava without reconstruction for urologic malignancies. Urology 2009;74:1257–1262.
43. Margulis V, Sanchez-Ortiz RF, Tamboli P, et al. Renal cell carcinoma clinically involving adjacent organs: experience with aggressive surgical management. Cancer 2007;109:2025–2030.
44. Capitanio U, Perrotte P, Zini L, et al. Nephrectomy improves survival in patients with invasion of adjacent viscera and absence of nodal metastases (stage T4N0 renal cell carcinoma). BJU Int 2009;104:795–799.
45. Karakiewicz PI, Suardi N, Jeldres C, et al. Neoadjuvant sutent induction therapy may effectively down-stage renal cell carcinoma atrial thrombi. Eur Urol 2008;53:845–848.
46. Di Silverio F, Sciarra A, Parente U, et al. Neoadjuvant therapy with sorafenib in advanced renal cell carcinoma with vena cava extension submitted to radical nephrectomy. Urol Int 2008;80:451–453.
47. Patard JJ, Thuret R, Raffi A, et al. Treatment with sunitinib enabled complete resection of massive lymphadenopathy not previously amenable to excision in a patient with renal cell carcinoma. Eur Urol 2009;55:237–239.
48. Thomas AA, Rini BI, Stephenson AJ, et al. Surgical resection of renal cell carcinoma after targeted therapy. J Urol 2009;182:881–886.
49. Thomas AA, Rini BI, Lane BR, et al. Response of the primary tumor to neoadjuvant sunitinib in patients with advanced renal cell carcinoma. J Urol 2009;181:518–523.
50. Paez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 2009;15:220–231.
51. Ebos JM, Lee CR, Cruz-Munoz W, et al. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 2009;15:232–239.
52. Bex A, Jonasch E, Kirkali Z, et al. Integrating surgery with targeted therapies for renal cell carcinoma: current evidence and ongoing trials. Eur Urol 2010; 58:819–828.
53. Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008;34:193–205.
54. Rini BI, Campbell SC. The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. J Urol 2007;177:1978–1984.
55. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–1659.

56. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–970.

57. Flanigan RC, Mickisch G, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071–1076.

58. Pantuck AJ, Belldegrun AS, Figlin RA. Nephrectomy and interleukin-2 for metastatic renal-cell carcinoma. N Engl J Med 2001;345:1711–1712.

59. de Reijke TM, Bellmunt J, van Poppel H, et al. EORTC-GU group expert opinion on metastatic renal cell cancer. Eur J Cancer 2009;45:765–773.

60. McDermott DF. Update on the application of interleukin-2 in the treatment of renal cell carcinoma. Clin Cancer Res 2007;13:716s–720s.

61. Spiess PE, Fishman MN. Cytoreductive nephrectomy vs medical therapy as initial treatment: a rational approach to the sequence question in metastatic renal cell carcinoma. Cancer Control 2010;17:269–278.

62. Thelen A, Jonas S, Benckert C, et al. Liver resection for metastases from renal cell carcinoma. World J Surg 2007;31:802–807.

63. Zerbi A, Ortolano E, Balzano G, et al. Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? Ann Surg Oncol 2008;15:1161–1168.

64. Piltz S, Meimarakis G, Wichmann MW, et al. Long-term results after pulmonary resection of renal cell carcinoma metastases. Ann Thorac Surg 2002;73:1082–1087.

65. Sherry RM, Pass HI, Rosenberg SA, et al. Surgical resection of metastatic renal cell carcinoma and melanoma after response to interleukin-2-based immunotherapy. Cancer 1992;69:1850–1855.

66. Kavolius JP, Mastorakos DP, Pavlovich C, et al. Resection of metastatic renal cell carcinoma. J Clin Oncol 1998;16:2261–2266.

67. Kim B, Louie AC. Surgical resection following interleukin 2 therapy for metastatic renal cell carcinoma prolongs remission. Arch Surg 1992;127:1343–1349.

68. Karam JA, Rini BI, Varella L, et al. Metastasectomy after targeted therapy in patients with advanced renal cell carcinoma. J Urol 2011;185:439–444.

69. Margulis V, McDonald M, Tamboli P, et al. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. J Urol 2009;181:2044–2051.

70. Logan T, McDermott D, Dutcher J, et al. Exploratory analysis of the influence of nephrectomy status on temsirolimus efficacy in patients with advanced renal cell carcinoma and poor-risk features [abstract]. Presented at the 2009 Genitourinary Cancers Symposium; February 26–28, 2009; Orlando, Florida. Abstract 281.