Controversies in the Surgical Management of Renal Cancer

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Abstract
Renal tumors are a common cause of cancer, and renal cell carcinoma accounts for the vast majority of the renal tumors in the United States. The past two decades have produced numerous advances in the treatment of localized and metastatic renal cell carcinoma. Nephron-sparing surgery, laparoscopic nephrectomy, and energy-ablative techniques are now in the armamentarium of the urologist. The role of adrenalectomy and lymphadenectomy are better understood today than in decades past, and recent advances in the understanding of immunotherapy, cytoreductive nephrectomy, and metastatic disease have also improved treatment for this disease. As is often the case as technology and knowledge evolve, controversies regarding the surgical treatment of renal cancer exist. This article outlines some of these controversies and reviews the evidence surrounding each. (JNCCN 2005;3:95–102)

Researchers estimate that 35,710 incident cases and 12,480 deaths from renal cancer occurred in the United States during 2004.1 The vast majority of renal tumors are renal cell carcinoma, and although improvements in imaging and treatment have led to a slight decline in mortality rates from renal cancer, the incidence of this disease in the United States continues to rise.1

The mainstay of therapy for localized renal cancer is so-called “radical nephrectomy.” Patients with small tumors confined to the kidney (stage T1; See the American Joint Committee on Cancer [AJCC] staging of Renal Cell Carcinoma, printed on page 7 of the NCCN Kidney Cancer Clinical Practice Guidelines in Oncology) show 5-year survival rates of more than 90%.1,2 The excellent prognosis for this subset of patients has led to the development of nephron-sparing surgical procedures, and advances in minimally invasive surgery have led to the proliferation of laparoscopic approaches to nephrectomy. Nephron-sparing, percutaneous, energy-ablative techniques are also being developed and finding their way into surgical practice.

Despite the excellent outcome associated with the surgical management of small localized tumors, patients with more advanced local disease can expect a 20% to 30% relapse rate.3 Given that renal cell carcinoma is not radio- or chemosensitive, strategies dealing with relapse have traditionally focused on surgical resection when possible. Similarly, in patients who present with metastatic disease, surgical resection has often been employed in the hopes of improving survival and quality of life. Recent randomized trials examining the benefit of immunotherapy in a monotherapy versus adjuvant setting have rekindled interest in cytoreductive nephrectomy for advanced disease in select patients.

As is often the case in surgical oncology, advances in surgical technique, technology, perioperative supportive care, and adjuvant therapy have resulted in controversies in the surgical management of both localized and metastatic disease. The goal of this review is to highlight these controversies and review the evidence surrounding each.

Localized Tumors
Radical Nephrectomy versus Elective Partial Nephrectomy
Radical nephrectomy through a large incision (“open” surgical approach) has long been the gold standard to
which all other treatments of localized renal cell carcinoma are compared. Though survival correlates to stage, patients with small tumors (T1a) have a greater than 95% 5-year cancer-specific survival rate.\(^2\) In the classic radical nephrectomy, the kidney, adrenal, perihilar tissue, and proximal ureter are excised en bloc within Gerota’s fascia. Radical nephrectomy usually also includes a lymphadenectomy, the extent of which varies from an area surrounding the renal hilum to an area encompassing wider fields surrounding both the venal cava and aorta. The need to preserve renal function in some patients, however, led to the development of nephron-sparing techniques of excising renal tumors. During partial nephrectomy, the tumor is resected along with a margin of normal renal parenchyma. Depending on the size, location, and nature of the tumor, the extent of the partial nephrectomy can range from hemi-nephrectomy to simple enucleation.

Partial nephrectomy first gained attention as a potentially elective procedure in the 1950s.\(^4\) However, cancer control rates were not as good as with radical nephrectomy, so the surgery fell out of favor as an elective procedure.\(^5\) Partial nephrectomy was still used when nephron sparing was desirable, such as for patients with solitary kidneys or bilateral tumors. Since the 1960s, improvements in surgical technique, imaging, and perioperative care have lead to expanded indications for nephron-sparing approaches. The absolute and relative indications for partial nephrectomy are generally well accepted\(^6\) (Table 1), but the indications for elective partial nephrectomy are more controversial.

No randomized studies comparing radical nephrectomy to elective partial nephrectomy have yet been completed, although several, most notably one in Europe, are currently underway. However, a number of recent large retrospective series have compared cancer-specific outcomes of radical nephrectomy with those of elective partial nephrectomy.\(^7\) These studies, which include more than 2,600 patients, show 5-year cancer-specific survival rates ranging from 89% to 98% for radical nephrectomy and from 89% to 100% for elective partial nephrectomy. All of these studies controlled for age, gender, and tumor size.

None of these studies showed a statistically significant difference in 5-year cancer-specific survival for patients with tumors smaller than 4 cm (stage T1a). Because of this, recommending a partial nephrectomy for T1a tumors in which the procedure is not technically difficult (tumors that are not centrally located) is generally accepted. The use of elective partial nephrectomy for stage T1b tumors (4–7 cm) is less certain. Two recent studies address this issue.

Leibovich et al.\(^8\) identified 932 patients who underwent nephrectomy for tumors 4 to 7 cm between 1970 and 2000. Of these patients, 91 underwent partial nephrectomy. After multivariate analysis, the authors found no difference in cancer-specific survival rates between patients treated with radical nephrectomy and those treated with partial nephrectomy. Similarly, Patard et al.\(^9\) reviewed the records of 641 patients from seven different academic centers in Europe, who underwent nephrectomy for tumors 4 to 7 cm between 1984 and 2001. After multivariate analysis, no difference in cancer-specific survival rates was found between 65 patients who underwent partial nephrectomy and 576 who underwent radical nephrectomy. These results suggest that elective partial nephrectomy may be a reasonable alternative in select patients with tumors larger than 4 cm.

Although overall major complication rates are similar when comparing radical nephrectomy with partial nephrectomy,\(^10\) partial nephrectomy exposes patients to a longer and technically more difficult surgery with an inherent set of risks. Stephenson et al.\(^11\) published the most contemporary series comparing complications in patients undergoing radical or partial nephrectomy. In review, of 1,049 patients treated between 1995 and 2002, 66% underwent radical

| Table 1 Indications for partial nephrectomy |
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| **Indication** | **Description** |
| **Absolute** | Radical nephrectomy would render the patient anephric (e.g., tumor in functionally solitary kidney, bilateral tumors). |
| **Relative** | Contralateral threatened by local disease (e.g., renal calculus, chronic pyelonephritis, ureteral reflux, renal artery stenosis). |
| | Contralateral kidney threatened by systemic disease (e.g., hypertension, diabetes, glomerulopathy). |
| | Genetic abnormalities that predispose the patient contralateral tumors (e.g., von Hippel-Lindau disease, young patients with a strong family history of renal tumors). |
nephrectomy. Overall, the complication rate was not different (16% for radical, 19% for partial; \( P = .3 \)). However, patients undergoing partial nephrectomy had a 5.5% chance of urinary fistula, and the perioperative re-intervention rate was 4 times higher in patients undergoing partial nephrectomy (0.6% vs. 2.5%; \( P = .02 \)). No difference was found in length of stay, need for blood transfusions, or major complications. These results are similar to less contemporary results reported by other investigators.\(^\text{10,13}\)

One of the major theoretical advantages of elective partial nephrectomy is the potential to protect against future chronic renal insufficiency by preserving a maximal amount of functioning renal parenchyma. At least two published studies support this possibility, although the assertion that renal preservation in the setting of a normal contralateral kidney leads to improved long-term renal function has never been definitively established. Lau et al.\(^\text{18}\) performed a matched analysis comparing results for patients who underwent radical nephrectomy and partial nephrectomy from 1966 to 1999. In that study, 164 patients in each cohort were matched based on tumor and patient characteristics as well as year of surgery. Longitudinal analysis showed the 10-year cumulative incidence of renal insufficiency (defined as a serum creatinine >2.0 mg/dL) to be 22% in the radical nephrectomy cohort and 12% in the partial nephrectomy cohort (\( P = .01 \)). McKiernan et al.\(^\text{19}\) retrospectively compared the records of 173 radical nephrectomy and 117 partial nephrectomy patients treated between 1989 and 2000. They found a 5-year cumulative incidence of renal insufficiency (defined as serum creatinine >2.0 mg/dL) of 15% in the radical group and 0% in the partial nephrectomy group (\( P = .008 \)).

The other potential benefit of elective partial nephrectomy is preservation of a functioning renal remnant in the event of a possible metachronous tumor in the contralateral kidney, the risk of which has traditionally been described as 4% to 15%. However, in a recent study looking at patterns of recurrence after radical and partial nephrectomy, Stephenson et al.\(^\text{3}\) reviewed the records of 495 patients and found only three metachronous contralateral renal recurrences. Furthermore, two of the three patients were found to have other distant sites of disease, and none of the 303 patients with initial stage T1 tumors developed contralateral recurrence. It is probably safe to conclude that contralateral recurrence is a relatively rare event, and the clinical significance of initial renal preservation in this group of patients is uncertain.

Taken as a whole, the evidence seems to support elective partial nephrectomy in patients with tumors smaller than 4 cm that are anatomically amenable to resection. The cancer-specific survival rates appear to be equal, and complication rates are comparable, although when widely applied, the rates are probably slightly higher than for radical nephrectomy. In fact, many surgeons in the urologic oncology community consider elective partial nephrectomy for stage T1a tumors the new “gold-standard.” We should emphasize, however, that removal of the whole kidney when the other kidney is normal is still an acceptable strategy.

In tumors larger than 4 cm, partial nephrectomy has a role for patients who meet the absolute and relative indications for partial nephrectomy. In the elective setting, however, the role of partial nephrectomy in patients with tumors larger than 4 cm is less clear. Although evidence exists that select patients with larger tumors do well after elective partial nephrectomy, further study and follow-up evaluation is needed in this subgroup of patients. This risk-to-benefit ratio for radical versus partial nephrectomy using the open approach is fast becoming obsolete, however, because of the introduction and dissemination of laparoscopic total and partial nephrectomy.

**Laparoscopic Nephrectomy**

In 1991, Clayman et al.\(^\text{20}\) reported the first successful laparoscopic nephrectomy. In successive years, laparoscopic techniques and instrumentation have improved, and the surgical skills necessary to perform this procedure have disseminated throughout the urologic community. Initially considered by some an onerous procedure that took many hours longer than its open equivalent, laparoscopic nephrectomy has become an important tool in the armamentarium of the urologic oncologist, with surgical times approaching those of open radical nephrectomy. Today, laparoscopic nephrectomy has become commonplace in academic centers, and is fast becoming a standard technique in community practices as well.

The main advantage of laparoscopic nephrectomy is decreased patient morbidity, which translates into shorter hospital stays and quicker recovery times. While the standard radical nephrectomy involves a
large flank incision, often with the resection of a rib, the laparoscopic approach requires only 3 or 4 port sites, ranging in size from 5 to 12 mm. The specimen is usually removed by extending one of the port sites 5 or 6 cm. But because this incision is on the abdomen, and usually in the midline, it is far less morbid than the often greater than 20 cm incision required when performing the open operation through the flank. Although no randomized comparison has been performed, several retrospective cohort studies have indicated markedly decreased blood loss, hospital length of stay, narcotic requirements, and convalescence after laparoscopic radical nephrectomy when compared with open surgery.21–23

The initial concerns about laparoscopic nephrectomy centered on cancer control and surgical times. However, with experience surgical times are approaching that of open surgery.21–23 Multiple studies have also confirmed that cancer control in laparoscopic radical nephrectomy is equivalent to that in open radical nephrectomy. Although published follow-up ranges from 2 to 4 years, cancer-free and overall survival rates appear to be equal for stage T1 and T2 tumors.21,24–27

Laparoscopic nephrectomy has now been accepted by most urologists as superior to open nephrectomy for stage T1 tumors. However, controversy exists when laparoscopic nephrectomy is compared with open elective partial nephrectomy. Small T1 tumors, which are most amenable to elective partial nephrectomy, are also most amenable to laparoscopic nephrectomy. Whether the decreased morbidity of a laparoscopic nephrectomy outweighs the potential benefits of nephron-sparing surgery in patients with a normal contralateral kidney is unclear and remains a matter of debate.

Also unclear is how dissemination of laparoscopy has affected the elective partial nephrectomy rate in the community. The controversy is further complicated by the introduction of laparoscopic partial nephrectomy.

Laparoscopic partial nephrectomy was initially described by McDougall et al.29 and has gained some popularity in centers where advanced laparoscopy is practiced. However, concerns remain about cancer control and complication rates during laparoscopic partial nephrectomy.29 When the procedure improves enough that results are similar for those open partial nephrectomy, it may supplant elective open partial nephrectomy as the gold standard for treating small renal tumors.

In summary, laparoscopic radical nephrectomy is preferred over open radical nephrectomy for T1a tumors, and may be preferred over open partial nephrectomy in this setting because of lower postoperative morbidity. The major yet unanswered question is whether laparoscopic partial nephrectomy can supplant laparoscopic radical nephrectomy as we gain more experience and techniques improve.

Energy-Based Ablative Techniques

The past 5 years have seen numerous techniques developed that deliver focal energy to renal tumors. Cryoablation, radiofrequency ablation, interstitial laser coagulation, high-intensity focused ultrasound, and microwave ablation attempt to treat the lesion while preserving surrounding normal renal parenchyma, usually through minimally invasive percutaneous approaches. Thus, these techniques have the potential to maximally preserve renal function with minimal morbidity.

However, several problems must be resolved before any of these techniques can be accepted as mainstream treatments for small renal lesions. First and most important, long-term follow-up is currently inadequate regarding morbidity and cancer control. Second but more immediate is the limited technical capacity to monitor the precise areas of energy delivery, creating the possibility of inadequately treated lesions. Finally, the natural history of the small asymptomatic lesions that these techniques are used for is unclear, and some data suggest that small tumors in patients not fit enough to undergo surgery may be safely followed up with serial imaging.8 Until these issues can be resolved, energy-ablative techniques should be considered experimental31 and reserved for select patients and in institutions that are formally investigating these techniques.

Adrenalectomy

In the classic description of the radical nephrectomy, the kidney and adrenal gland are excised en bloc within the investing Gerota’s fascia. Conventional wisdom regarding the role of adrenalectomy for localized disease, however, has evolved since the original description of the surgery. In three contemporary series that together include more than 2,000 patients, the incidence of adrenal metastases ranged from 3.1% to 5.5%.12–14 Furthermore, the vast majority of patients...
with adrenal involvement (>80% in all three studies) had stage T3 disease or greater at time of nephrectomy. Upper pole location of the tumor was also predictive of adrenal involvement.

The accuracy of modern preoperative cross-sectional imaging also assists in evaluating patients for adrenal metastases. Adrenalectomy is therefore considered necessary only in cases with large tumors, upper pole involvement, or preoperative or intraoperative evidence of adrenal involvement.

**Lymphadenectomy**

The role of lymphadenectomy during nephrectomy for renal cancer is controversial. Experts recognize that lymph node metastases portend a poor prognosis. However, whether surgical removal of involved lymph nodes conveys an improved prognosis is less clear. Blom et al. reported on the results of the only randomized trial evaluating the benefit of lymphadenectomy at radical nephrectomy. They randomized 772 patients to either receive nephrectomy alone or nephrectomy plus a standardized regional lymph node dissection. Based on the inclusion criteria none of the patients had evidence of preoperative lymph node involvement of metastases based on CT, urogram, and chest radiograph. They found that the incidence of lymph node metastases in this group was 3.3%. They also found that even in the presence of palpably abnormal lymph nodes, the incidence of metastases was only 16%. After 5 years of follow-up, the overall survival rate in the two arms is 82% and not significantly different. Lymphadenectomy did not appear to add morbidity.

At least one large observational study has suggested a potential benefit to lymphadenectomy. Pantuck et al. performed a retrospective cohort study and evaluated the records of 900 patients whose lymph node status was known and who underwent nephrectomy. They found no difference in survival among patients with clinically localized tumors who underwent lymphadenectomy compared with patients who did not. However, the authors also found that patients with metastatic disease who underwent cytoreductive nephrectomy plus lymphadenectomy had significantly improved survival with immunotherapy than those who underwent cytoreductive nephrectomy alone. These results are consistent with other reports that patients with known lymph node metastases do poorer with immunotherapy compared to those who do not.

Although the evidence is far from overwhelming, it seems reasonable to perform lymphadenectomy at the time of radical nephrectomy in select circumstances. Specifically, given that few therapeutic alternatives exist, lymphadenectomy may be beneficial when in the setting of suspected lymph node involvement when lymph nodes are surgically accessible and resection does not risk undo morbidity. Most urologic oncologists limit the extent of the lymphadenectomy to the area immediately surrounding the renal hilum unless evidence of tumor involvement is found, in which case some, but not all, oncologists perform a wider dissection. Of course, the surgeon must also consider the possibility of falsely positive nodes and balance this against the risk of pursuing lymph nodes that may be difficult to resect. Based on the available evidence, lymphadenectomy does not seem warranted in tumors clinically localized to the kidney.

**Metastatic Disease**

**Role of Nephrectomy**

Researchers estimate that 20% to 30% of patients with renal cell carcinoma present with metastatic disease and that 20% to 40% of patients who undergo nephrectomy for localized disease will ultimately develop metastases. Despite advances in treating localized renal cell carcinoma, patients with metastatic disease still face a dismal prognosis, with an estimated 5-year survival rate of 10%. Metastatic renal cell carcinoma is both chemotherapy and radiation resistant, leaving few alternatives for patients with metastases. However, with the application of immunotherapy in the past 10 years, the outlook has improved for some patients with metastatic disease.

Immunotherapy for renal cell carcinoma usually consists of either interferon-α or interleukin-2 (IL-2). The benchmark trial that showed a positive effect of immunotherapy evaluated IL-2 therapy in 255 patients with metastatic renal cell carcinoma. This phase II trial showed an overall objective response rate of 14%, with a 9% partial and 5% complete response rate. Subsequent analysis showed these response rates to be durable, with a greater than 80-month median duration in the complete response group.
remained, however, on whether a role exists for nephrectomy before immunotherapy administration.

Nephrectomy in the setting of metastatic disease has traditionally been reserved as a palliative procedure or for patients who had metastatic disease that was amenable to complete resection. However, with the advent of immunotherapy, some investigators advocated cytoreductive nephrectomy before adjuvant immunotherapy. The potential advantages of cytoreductive nephrectomy include getting tissue for treatment protocols and prevention of further metastases. Researchers have also postulated that reducing tumor volume may make the residual tumor more susceptible to treatment with immune modulating agents. Observational studies appeared to show benefits for cytoreductive nephrectomy, the largest of which showed that surgery could be performed safely.

However, in this study, only 62% of patients eligible for IL-2 received it after nephrectomy, because of tumor progression, renal insufficiency, death, or refusal. This result fueled debate on whether surgery should be reserved for patients who respond well to IL-2, thus avoiding unnecessary surgical morbidity and cost for patients who are less likely to show a response to systemic treatment and have a favorable outcome. Fortunately, recent randomized studies have shed light on this issue.

In 2001, Mickisch et al. reported on the results of an EORTC trial that randomized 85 patients with metastatic renal cell carcinoma to receive cytoreductive nephrectomy followed by interferon-α or interferon-α alone. They showed that the nephrectomy group had an improved median survival of 17 months versus 7 months in the interferon alone group (P = .03). Objective response rates were 19% and 12% in the surgery and non-surgery groups, respectively (P = .38).

Two months later, Flanigan et al. reported on the results of the SWOG companion study, which had the same eligibility requirements and treatment protocols as the EORTC study. In the SWOG study, 241 patients were randomized and similar results were seen. Median survival was 11.1 months in the surgery group and 8.1 months in the interferon group (P = .05). In both studies, performance status was a strong predictor of outcome, regardless of treatment arm. In addition to improved survival, these studies showed the safety of surgery and the ability of surgical patients to undergo immunotherapy (only 5.6% of surgical patients in these studies did not receive adjuvant interferon-α). This shows the importance of patient selection, namely a WHO performance status of 0 or 1 and a lack of comorbid conditions that would make them high-risk surgical candidates.

Although the outcomes in metastatic renal cancer remain less than ideal, these studies show a role for cytoreductive nephrectomy and adjuvant immunotherapy in well selected patients. In patients with unresectable metastatic disease who are not candidates for immunotherapy, nephrectomy should rarely be necessary and should be reserved for palliative purposes only.

Metastectomy
As noted previously, up to 30% of patients with renal cancer will present with metastatic disease. A significant proportion of these patients will have metastatic disease that is amenable to surgical resection, and a further subset of patients will develop metastases after nephrectomy for apparently localized disease. Debate exists as to whether surgical resection should be performed in either of these settings.

The concept of removing solitary metastases at the time of initial nephrectomy was popularized in the 1970s and 5-year survival rates were found to be 29% to 35%. Since then, several series have reinforced the potential benefit of resecting metastases. Kierney et al. reported on 41 patients with a solitary metastatic focus who underwent surgical resection at a median time of 27 months after nephrectomy. In this series, the median survival was 3.4 years, with 5-year survival estimates of 31%. At least one patient in this series was alive 93 months after the first of 12 separate metastectomies.

In a larger series, Kavolius et al. reviewed the records of 278 patients with recurrent renal cell carcinoma. They found that solitary recurrence, longer disease-free interval after nephrectomy, and younger age were associated with improved outcomes. The overall 5-year survival rate for 141 patients who underwent complete metastectomy was 44%. The 5-year survival rate was only 14% in patients who did not undergo complete resections, and was 11% in patients treated non-surgically. Given that the prognosis of metastatic renal cell carcinoma is poor and that complete resection of low-volume metastatic disease is likely to achieve positive results in some
patients, metastectomy is a reasonable approach in select patients.

Conclusions
The treatment of renal cancer has evolved rapidly in the past several decades. Most of the advances have revolved around the treatment of localized tumors using nephron-sparing and minimally invasive techniques. However, advances in our understanding of systemic immunotherapy, cytoreductive surgery, and metastatic disease have also improved our ability to manage this disease. The controversies that revolve around some of these issues should be interpreted as a sign of progress and understanding, because controversies in management only exist with the advent of new therapies and approaches. History dictates that we should welcome new controversies surrounding this disease as the current controversies are resolved through experience and scientific study.

References


