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Advanced Stage Renal Cell Carcinoma Treated by Radical Nephrectomy and Adjacent Organ or Structure Resection

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Abstract

Introduction and Objective—Invasion of adjacent organs in patients with renal cell carcinoma (RCC) is rare. The purpose of our study was to examine the impact of radical nephrectomy (RN) with adjacent organ and structure resection on survival.

Methods—After institutional review board approval, a database review and statistical analysis of patients with pathologic stage T3 or T4 RCC who underwent RN and resection of a contiguous organ or structure was performed.

Results—We identified 38 patients out of 2464 (1.5%) who underwent RN with adjacent organ or structure resection. Median mass size was 11 cm (IQR=8, 14 cm). Median follow-up was 13 months (IQR=5, 33 months). The majority of patients (68%) were pT4 stage and had conventional clear cell carcinoma (95%). Fourteen patients (37%) had positive surgical margins. The liver (10) was the most commonly resected adjacent organ or structure. Only 1 patient remains alive without evidence of disease at 5 years, while 3 patients are currently alive with disease. The overall mortality rate was 34 of 38 patients (90%). The median time from surgical resection to death was 11.7 months (IQR=5.4, 29.2 months). The surgical margin status was the only statistically significant factor for recurrence and death ($p=0.0061$).

Conclusions—The prognosis of advanced RCC patients with adjacent organ or structure involvement is extremely poor and similar to patients with metastatic disease. These patients should be thoroughly counseled regarding the impact of surgical management and considered for entry into neoadjuvant or adjuvant clinical trials with new targeted systemic agents.

Keywords

renal cell carcinoma; adjacent organ resection; advanced local renal cell cancer

Introduction

It is estimated that in 2008 that approximately 54,000 patients will be diagnosed with renal cell cancer (RCC) and an estimated 13,000 patients will die of their disease[1]. The majority of these deaths occur in patients who present with large, locally advanced tumors that have already or will soon metastasize. The overall survival for patients with locally advanced large renal cortical tumors (RCT) or metastatic disease is generally poor with 5 year survival rates less than 10%[2]. Partial or radical nephrectomy remain the established treatment for small (T1) renal lesions; while, patients with large, locally advanced (T3 or T4) lesions are often labeled

as “unresectable” and not offered operative intervention. However, the recent introduction of targeted molecular therapies [3,4] with their potential to delay tumor progression, a cohort of patients who present with locally advanced disease now have a viable treatment option after surgical management of the primary tumor. The optimal role and timing of radical nephrectomy with adjacent organ resection in patients with T4 disease remains controversial [4-7]. The purpose of our study was to review our institutional experience with radical nephrectomy and adjacent organ resection in patients with locally advanced renal cortical tumors prior to the era of targeted therapy.

Materials and Methods

After obtaining Institutional Review Board approval, a review of our prospectively collected renal surgical database was performed for all patients treated with radical nephrectomy for RCT from December 1989 to April 2006. Of the 2464 nephrectomies (938 partial and 1526 radical) performed during this period we identified 38 patients with pathologic stage T3 or T4 disease with concomitant adjacent organ resection at the time of their nephrectomy meeting our inclusion criteria. The definition of an adjacent organ consisted of resection of a neighboring structure that was involved by direct extension of the tumor excluding the ipsilateral adrenal gland. Relevant clinical, radiographic, and pathological data were collected and maintained in a secure database. All patients were evaluated pre-operatively with complete physical examinations, routine laboratory analysis, and pre-operative imaging with CT or MRI scans. All operations were performed at our institution by one of 11 surgeons. RCT staging was performed according to the AJCC 2002 TNM classification [8] with tumor histology assigned according to the 2004 WHO criteria [9] after review by dedicated genitourinary pathologists at our institution. Follow-up visits and treatment plans were determined based on the final pathology and margin status of the surgical specimen. During the time of our analysis adjuvant therapies consisted on interferon- α , interleukin-2, suramin, cis-retinoic acid, and sunitinib. Univariate and multivariate analysis were performed for data evaluation. Survival distributions were determined by the Kaplan-Meier method. P-values less than 0.05 were considered significant. Analyses were conducted using Stata 8.2 (Stata Corp., College Station, TX).

Results

During the time period from December 1989 to April 2006, 38 patients underwent radical nephrectomy with resection of at least 1 adjacent organ at our institution for renal cortical masses. Pre-operatively, 33 of 38 patients (87%) were aware that surgical treatment would involve removal of an adjacent structure. Twenty-six patients (68%) presented with clinical stage T4 disease with the median tumor size for all patients of 11cm (IQR=8, 14cm). Cohort and surgical characteristics are presented in Table 1. Final pathology revealed conventional clear cell carcinoma in 36 (95%) patients, with 24 (63%) patients having evidence of sarcomatoid features on final pathology. Seventeen patients (45%) had 1 adjacent organ resected at the time of nephrectomy, 13 (34%) had 2 neighboring structures removed, and 8 patients (21%) had 3 adjacent organs removed. The most common organs resected were liver (10), IVC (9), vertebral body (8), pancreas (6), bowel (6), spleen (3) and psoas (2). All resected organs revealed direct tumor invasion. Thirty-four patients (90%) had resection of the ipsilateral adrenal gland, with 13 (34%) of these patients having direct extension of their RCT into the adrenal. Thirty of 38 patients (79%) had a regional lymphadenectomy performed at the time of their nephrectomy with 8 of these patients (27%) having node positive disease.

Fourteen patients (37%) had positive surgical margins on final pathology which correlated with a significant difference in survival ($p=0.0061$). There were 2 peri-operative deaths, 3 people alive with disease, and 1 patient currently alive without disease at 60 months (figures 1a and

1b). Overall, 34 of 38 patients in our cohort are deceased at the time of analysis with median survival from surgery to death being 11.7 months (IQR=5, 29 months). Eighteen patients (47%) received adjuvant medical therapy after surgery, 15 of which died from disease and 3 patients died from other causes. Eight patients received interferon monotherapy, 4 patients were given interferon with interleukin-2, and two patients received cis-retinoic acid (as part of a clinical trial). Suramin and sorafenib were given to 1 patient each. Seven patients received adjuvant radiation therapy for palliation of metastatic bone lesions. In terms of overall survival outcomes, surgical margin status (figure 2) was the only statistically significant factor ($p=0.0061$) among variables including number of organs resected ($p=0.438$), high pathologic grade ($p=0.9307$), sarcomatoid status ($p=0.761$), adrenal involvement ($p=0.3696$) and size of tumor greater than 7cm ($p=0.29$).

Discussion

The results of our study demonstrate that radical nephrectomy with resection of adjacent organs for RCTs is a rare intervention (1.5% of all nephrectomies performed) with most of these patients having very poor survival. This is not unexpected since the majority of patients in our study (90%) presented with either local or systemic symptoms from their tumor. Historically, it is accepted that approximately 30% of patients will present metastatic disease or soon thereafter develop metastatic disease [10], with the incidence of metastasis increasing with larger primary tumor size [11]. In a recent international multicenter study of 2245 patients who were treated with radical nephrectomy for clear cell RCTs, Karakiewicz et al found that size was a significant predictor of recurrence [11]. Larger tumor sizes predispose to metastatic disease which portends a poor prognosis with 5 year survival rates being less than 10% [12].

The decision to operate on large, locally advanced tumors is often difficult and controversial given the poor long-term prognosis. Some feel the risks of a radical nephrectomy with complex resection of adjacent organs do not justify the small potential benefit. In a recent publication on selection criteria for cytoreductive nephrectomy, an inoperable tumor was considered to have “invasion of adjacent tissues or organs with an associated confluent nodal mass involving the great vessels...but not including the renal vein or IVC” [13]. In that study, only 40% of the patients were deemed operable candidates and if those criteria were applied to our cohort, none of our patients would have been considered operative candidates. In addition to anatomic factors influencing patient selection, recent criteria described by Motzer et al [14], including Karnofsky performance status, lactate dehydrogenase level, serum hemoglobin level, corrected serum calcium can assist in the selection of appropriate surgical candidates. If the decision to operate is made then the optimal treatment for these large, locally advanced RCTs consists of radical nephrectomy with removal of perinephric soft tissues, ipsilateral adrenal gland, regional lymphadenectomy, and possible resection of the IVC [15]. Additionally, if intraoperative findings demonstrate extension of the tumor into an adjacent organ, then resection should be performed in an attempt to obtain complete tumor removal. In our series, 14 patients (37%) had positive surgical margins, which was the only significant factor ($p=0.0061$) impacting survival.

The decision not to operate is largely based on radiographic imaging which can often over-stage RCTs. Margulis et al recently demonstrated that patients with large RCTs who were thought to have adjacent organ involvement on pre-operative imaging were in fact over-staged 60% of the time. Only 12 of 30 patients (40%) actually had true pT4 disease into an adjacent structure or organ demonstrated at nephrectomy [16]. In our series, 26 of 38 patients (68%) had pT4 disease predicted by pre-operative imaging. Similar to our series, an overwhelming majority of these patients (10 of 12 patients, 83%) developed recurrent disease at a median time of recurrence of only 2.3 months. In their cohort, five patients are currently alive at the time of analysis.

In addition to size, there are several established factors that predispose to recurrence of renal cell cancer including: higher Fuhrman grade[17], histologic subtype, node status and presence of sarcomatoid features[18]. Likely due to the small sample size we were unable to demonstrate these factors impacting survival in our study. Patients with adrenal involvement ($p=0.3696$) and those who had a greater number of organs resected ($p=0.438$) followed a trend towards worse survival, but this did not reach statistical significance.

Data supporting radical nephrectomy with adjacent organ resection can be extrapolated from the 2001 studies by the Southwest Oncology Group (SWOG) and the European Organization Research and Treatment of Cancer (EORTC) demonstrating a survival advantage for patients with metastatic disease who had undergone cytoreductive nephrectomy plus adjuvant treatment with interferon alfa 2b versus interferon alone. The surgical group had a median survival of 13.6 months versus 7.8 months for the group treated with interferon alone[5]. Earlier work from our institution also demonstrated that complete resection of all sites of disease was associated with improved survival. Those patients who had a complete metastasectomy along with nephrectomy had a median survival of 30 months compared to 12 months in those who were treated with cytoreductive nephrectomy alone [2].

The recent introduction of novel antiangiogenic agents has provided new hope for patients with metastatic disease. In a recent international multicenter, randomized phase III study, Motzer, O'Brien, et al report favorable responses with sunitinib in a cohort of patients with metastatic clear cell renal cancer who failed prior cytokine therapy. Thirty-one percent of sunitinib treated patients had objective responses compared to only a 6% response rate in patients treated with interferon- α ($p<0.001$) [19]. No complete responses were observed, however progression free survival was nearly doubled in the sunitinib group relative to the interferon- α treated patients (11 vs. 5 months HR 0.42, $p<0.001$) [19]. While there were no durable cures, these findings are encouraging and should be considered when counseling patients with locally advanced RCT if surgery is planned. Surgical resection of the local tumor could be considered as part of a multi-modal approach in the treatment of patients with locally advanced RCTs.

There are currently 4 patients still alive in our series during the present follow-up period. One patient has no evidence of disease 6 years after radical nephrectomy and resection of liver involvement and negative lymph nodes for a sarcomatoid RCC (figure 2). The other 3 patients are currently alive with disease 4, 2, and 1 years respectively after their operation. Despite the majority of our patients having negative surgical margins, our patients incurred a 76% recurrence rate and 90% mortality rate for our entire cohort within the time of follow-up. Our recurrence rate was similar to the MD Anderson series (83% recurrence in pT4 patients) [16]. These results suggest that patients with locally advanced RCTs who undergo complex resection of adjacent organs at the time of radical nephrectomy have poor outcomes similar to those patients with metastatic disease.

Patients who present with locally advanced RCTs should be thoroughly counseled regarding the natural history of their disease and the overall poor prognosis. However, they should not be automatically excluded from surgical consideration. The role of surgical intervention for advanced local disease will continue to evolve as new treatments for recurrent disease are discovered. The recent studies on sorafenib and sunitinib, demonstrating disease stabilization and delay in progression may provide additional treatment options for those patients who develop metastatic disease after radical nephrectomy [20,21].

The retrospective method and small number of patients in our study are acknowledged limitations of our study. During the study period, our tertiary referral center performed 2464 nephrectomies (938 partial and 1526 radical) for RCTs with only 38 patients meeting inclusion

criteria, thereby identifying the rarity of adjacent organ involvement and the need for aggressive resection at the time of radical nephrectomy.

Conclusions

Overall, a small number of patients with renal cortical tumors will present with locally advanced disease that will require complex surgery with adjacent organ resection. For those patients who have radical nephrectomy with adjacent organ resection, surgical margin status is the most important variable in determining overall survival. These patients often have survival outcomes similar to patients with metastatic disease and should be considered for neoadjuvant or adjuvant clinical trials.

References

1. Jemal, A.; Siegel, R.; Ward, E., et al. Cancer statistics. Vol. 58. a cancer journal for clinicians; CA: Mar-Apr. 2008 p. 71-96.2008
2. Russo P, Synder M, Vickers A, Kondagunta V, Motzer R. Cytoreductive nephrectomy and nephrectomy/complete metastasectomy for metastatic renal cancer. *The Scientific World Journal* 2007;7:768–78.
3. Tamaskar I, Garcia JA, Elson P, et al. Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. *The Journal of urology* Jan; 2008 179:81–6. [PubMed: 17997441]discussion 6
4. Motzer RJ, Michaelson MD, Rosenberg J, et al. Sunitinib efficacy against advanced renal cell carcinoma. *The Journal of urology* Nov;2007 178:1883–7. [PubMed: 17868732]
5. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *The Journal of urology* Mar;2004 171:1071–6. [PubMed: 14767273]
6. 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. *The New England journal of medicine* Dec 6;2001 345:1655–9. [PubMed: 11759643]
7. Mickisch GH, Garin A, van Poppel H, de Pijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* Sep 22;2001 358:966–70. [PubMed: 11583750]
8. Greene FL. The American Joint Committee on Cancer: updating the strategies in cancer staging. *Bulletin of the American College of Surgeons* Jul;2002 87:13–5. [PubMed: 17387902]
9. Eble, JNSG.; Epstein, JI.; Sesterhenn, IA. Tumors of the urinary system and male genital organs. IARC Press; Lyon: 2004. Pathology and genetics.
10. Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. *Cancer* Nov;1971 28:1165–77. [PubMed: 5125665]
11. Karakiewicz PI, Lewinshtein DJ, Chun FK, et al. Tumor size improves the accuracy of TNM predictions in patients with renal cancer. *European urology* Sep;2006 50:521–8. [PubMed: 16530322]discussion 9
12. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *The New England journal of medicine* Sep 19;1996 335:865–75. [PubMed: 8778606]
13. Bromwich E, Hendry D, Aitchison M. Cytoreductive nephrectomy: is it a realistic option in patients with renal cancer? *BJU international* Apr;2002 89:523–5. [PubMed: 11942956]
14. Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. *J Clin Oncol* Jul 1;2006 24:3101–6. [PubMed: 16809736]
15. Russo, P. Genitourinary Oncology. In: Vogelzang, N., editor. Open radical nephrectomy for localized renal cell carcinoma. Vol. 3rd edn.. Lipincott Williams and Wilkins; Philadelphia, PA: 2006. p. 725-31.

16. Margulis V, Sanchez-Ortiz RF, Tamboli P, Cohen DD, Swanson DA, Wood CG. Renal cell carcinoma clinically involving adjacent organs: experience with aggressive surgical management. *Cancer* 2007;109:2025–30. [PubMed: 17420980]
17. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. *The Journal of urology* Jan; 2005 173:48–51. [PubMed: 15592023]
18. Lam JS, Beldegrun AS, Pantuck AJ. Long-term outcomes of the surgical management of renal cell carcinoma. *World journal of urology* Aug;2006 24:255–66. [PubMed: 16479388]
19. O'Brien MF, Russo P, Motzer RJ. Sunitinib therapy in renal cell carcinoma. *BJU international* Jun; 2008 101(11):1339–42. [PubMed: 18284408]
20. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *Jama* Jun 7;2006 295:2516–24. [PubMed: 16757724]
21. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* Jun 1;2006 24:2505–12. [PubMed: 16636341]

Figures 1a and 1b.

Figure 1a Kaplan Meier Overall Survival

Figure 1b Kaplan Meier Overall Survival According to Surgical Margin Status.

Figure 2.
Pre-operative CT demonstrating extensive tumor with local invasion into the liver. This patient is currently alive without evidence of disease.

Table 1

Patient Demographics		n=38 # (%) or median(IQR)
Age (years)		63 (49, 70)
Gender	Male	27 (71%)
	Female	11 (29%)
Presentation	Incidental	3 (8%)
	Local Symptoms	21 (55%)
	Systemic Symptoms	13 (34%)
	Unknown	1 (3%)
Laterality	Right	24 (63%)
	Left	14 (37%)
Presenting Clinical Stage		
T3		12 (32%)
T4		26 (68%)
Tumor Size (cm)		11 (5, 33)
Histologic Subtype	Conventional (clear cell)	36 (95%)
	Papillary	2 (5%)
	Sarcomatoid features	24 (63%)
		n=33
Tumor Grade	Grade 1-2	3 (9%)
	Grade 3-4	30 (91%)
Surgical margin status		
Positive		14 (37%)
Negative		24 (63%)
Number of adjacent organs resected		
1		17 (45%)
2		13 (34%)
3		8 (21%)
Adjacent organ resected		
Liver		10
IVC		9
Vertebral body		8
Pancreas		6
Bowel (large and small)		6
Spleen		3
Ipsilateral adrenal resection		34 (90%)
Direct extension into adrenal		13 (34%)
Positive lymph nodes		8 (27%)
Time of follow-up (months)		13.1 (5, 33)
Time from surgery to death (months)		11.7 (5, 29)