

## MANAGEMENT OF ISOLATED RENAL FOSSA RECURRENCE FOLLOWING RADICAL NEPHRECTOMY

VIRAJ A. MASTER, ALEXANDER R. GOTTSCHALK, CHRISTOPHER KANE  
AND PETER R. CARROLL<sup>\*,†</sup>

*From the Department of Urology, Department of Radiation Oncology (ARG), and UCSF Comprehensive Cancer Center, University of California, San Francisco*

### ABSTRACT

**Purpose:** Local recurrence of renal cell carcinoma in the renal fossa without distant metastatic disease is an infrequent occurrence. Management of this lesion can be challenging, with relatively few series in the literature. We describe our use of surgical extirpation with adjuvant intraoperative radiation.

**Materials and Methods:** The University of California, San Francisco Urologic Oncology database and the University of California, San Francisco Radiation Oncology database were queried for all patients with locally recurrent renal fossa recurrence. Only patients with recurrence of renal cell carcinoma in the renal fossa were included. Survival, complications and the use of adjuvant therapy in the form of intraoperative radiation therapy were noted.

**Results:** A total of 14 patients were treated for this lesion between 1990 and 2003. Mean time to recurrence was 40 months (range 5 to 180). Only 1 patient was symptomatic preoperatively, while in 13 disease had been detected on routine computerized tomography followup. Mean size of the recurrent tumor was 6.35 cm (range 2 to 17). 9 patients died of progressive, metastatic disease after a mean of 17 months (range 1 to 56) and 5 are alive with a mean survival of 66 months (range 14 to 86). The time to recurrence after nephrectomy approached statistical significance ( $p = 0.06$ ) when comparing the patients who were alive vs those who died of disease. Additionally, there was no statistical difference in size of mass recurrence between these 2 groups. There was no difference in survival due to adjuvant intraoperative radiation therapy. Local fossa re-recurrence developed in 2 patients. Survival was 40% at 2 years and 30% at 5 years from surgery. Complications, including minor complications, occurred in 42% of patients and there was no perioperative mortality.

**Conclusions:** Selected patients with isolated local recurrence in the renal fossa may have favorable and durable outcomes following surgical resection and possibly adjuvant intraoperative radiation therapy for isolated renal fossa recurrence following radical nephrectomy. Development of novel and effective systemic therapy is needed in high risk patients with renal cancer.

**KEY WORDS:** carcinoma, renal cell; recurrence, radiotherapy

Renal cell carcinoma (RCC) is relatively common malignancy with an estimated 35,710 new cases of kidney cancer (22,080 in men and 13,630 in women) in the United States in 2004, with approximately 12,480 deaths (7,870 men and 4,610 women) from this disease.<sup>1</sup> Presently, this malignancy is best managed by surgery, with multiple extirpative options have been developed to treat this malignancy, including laparoscopic radical nephrectomy, open partial nephrectomy and laparoscopic partial nephrectomy, as well as conventional open radical nephrectomy. Additionally, ablative therapy with cryotherapy, radiofrequency or thermal ablation delivered via open, laparoscopic or percutaneous approaches, has been performed.<sup>2</sup>

The majority of patients treated for T1/T2 lesions with surgery will be cured and predictors of outcome based on pretreatment and pathological characteristics have been developed.<sup>3–5</sup> However, patients can fail their initial therapy,

with progressive metastatic disease, especially pulmonary or osseous metastases, or with the development of local recurrence. The incidence of pure local fossa recurrence ranges widely in the literature from 1% to 37%, with most modern series having an approximately 1% to 2% local recurrence rate, as older series include local recurrences in the presence of distant metastatic disease.<sup>6,7</sup>

There is no standard treatment for this rare event. There have been a few case series of the treatment of local recurrence of kidney cancer. Some of these series encompass a heterogeneous population of patients including those with renal malignancies which are not RCC.<sup>8</sup> Others include patients with local-regional recurrence including lymph node recurrences or the presence of resected distant metastatic disease, or even no malignancy found on exploration.<sup>9</sup> There are a subset of patients with relatively long-term survival, but significant morbidity and even mortality was encountered, especially in early, series.<sup>8</sup> We sought to study a homogenous well characterized series of patients with local fossa recurrence, who were all treated with surgery, as well as some treated with adjuvant intraoperative radiation therapy. The morbidity of the procedure and long-term outcomes are described.

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\* Correspondence: Department of Urology, 1600 Divisadero St., Box 1695, San Francisco, California 94143-1695 (e-mail: pcarroll@urol.ucsf.edu).

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## MATERIALS AND METHODS

The University of California, San Francisco (UCSF) Urologic Oncology Database, which contains more than 450 data elements per patient, was queried for patients who underwent surgical resection for locally recurrent renal cell carcinoma between 1990 and 2003 to acquire the study population. In addition, the UCSF Department of Radiation Oncology database was queried for all patients who received radiation therapy for locally recurrent renal cell carcinoma. Patient status was also checked using the UCSF Tumor Registry database, including determining cause of death, if applicable. Patients who had local recurrence and distant metastatic disease were excluded to provide a homogenous population.

All patients were evaluated with computerized tomography of the chest, abdomen and pelvis, as well as whole body bone scans to select patients with only a local fossa recurrence. Blood count and serum chemistries were drawn preoperatively. Surgical reports and pathology slides were reviewed at the UCSF Comprehensive Cancer Center. Following treatment, patients were closely followed with serial imaging studies and office visits. The main outcome measures were overall survival and perioperative complications. Statistical analysis was performed using a 2-tailed t test.

## RESULTS

A total of 14 patients were identified as having undergone treatment for local fossa recurrence of renal cell carcinoma, comprising 10 men and 4 women (table 1). No patients were identified as having pure local recurrence who were treated with radiation alone. Our surgical database did not record whether patients with isolated local fossa recurrence were not offered surgery, but as a faculty practice, all patients with isolated local recurrence were offered surgery. The mean age of patients at time of initial radical nephrectomy was 51.6 years (median 54, range 16 to 68). All patients were diagnosed by cross-sectional imaging and were clinically staged as T2 kidney cancers. All patients except 1 were believed by their referring urological surgeon to have a complete resection, although 3 cases had positive surgical margins and 1 case had fluid spillage from a large cystic renal cell carcinoma. Surgical pathology showed pT1 pathology in 2 patients, pT2 in 2 and pT3 in 10 (1997 TNM classification). Only 1 patient had lymph node invasion on pathological examination. Tumor histology was significant for 1 patient with a collecting duct carcinoma, 2 with papillary and sarco-

matoid histology and the rest with either clear cell or papillary renal cell carcinoma. Fuhrman grade distribution varied with 2 patients with Fuhrman grade 1 (G1) cytological features, 3 with G2, 5 patients with G3 and finally 4 patients with G4 cytology. The mean Fuhrman grade of patients who died was 3.22 vs grade 2 for the surviving patients, which did not reach statistical significance ( $p = 0.07$ ).

Following initial radical nephrectomy, patients presented with the presence of a growing mass on cross-sectional imaging. Only 1 patient also had symptomatic complaints of new and increasing incisional, back and flank pain. The mean time to recurrence was 40 months (median 26.5, range 5 to 180). The mean time to recurrence between patients who died was 16 months (range 5 to 34) vs 83 months (range 32 to 180) for those who did not die, which approached statistical significance ( $p = 0.06$ ). At the time of diagnosis, Karnofsky Performance Score was 90 to 100 in all patients, except 1 man who had a score of 50. Only 1 patient had leucocytosis/thrombocytosis and otherwise mean laboratory values were unremarkable. The size of the recurrent mass was  $6.35 \pm 4.4$  cm (median 5, range 2 to 15).

All patients underwent complete extirpation of the recurrent mass, generally extending their old incision site to a chevron-type incision. The masses tended to have ill-defined margins and often involved adjacent structures (table 1), which were removed en bloc when obviously involved. Operative times averaged 450 minutes and the mean blood loss was 1,700 cc (but was not recorded for 3 patients). The median transfusion requirement was 1 unit of packed red blood cells. The mean hospital stay was 9.2 days and 6 patients required an intensive care unit stay averaging 1.6 days.

Complications ensued in 6 (42%) of patients. The most common complication was pancreatic leak following partial pancreatectomy in 4 patients (29%). In all of these cases, management was nonoperative, usually involving the placement of percutaneous drains and intravenous antibiotics. Additional complications included diarrhea in 1 patient, ileus in 1 patient and prolonged intubation/pneumonia in 1 patient.

A majority of patients received some form of neoadjuvant or adjuvant therapy. Preoperative chemotherapy/immunotherapy was given to 5 patients, although only 1 patient was able to complete a full course of the interleukin-2 based therapy. There were 10 patients (71%) who received intraoperative radiation therapy (IORT), with a mean dose of 1,500 cGy (median 1,500, range 1,200 to 2,000). Early in the series

TABLE 1. Patient characteristics

| Age | Cell Type               | Grade | Mos Recurrence | Mass Size (cm) | Neoadjuvant Immunotherapy | IORT (cGy) | Adjunctive Procedures + Mass Excision                              | Death (mos) | Last Followup (mos) |
|-----|-------------------------|-------|----------------|----------------|---------------------------|------------|--|-------------|---------------------|
| 56  | Papillary               | 3     | 13             | 8              |                           | 1,200      |  |             | 100                 |
| 17  | Papillary               | 3     | 32             | 2              |                           |            |  |             | 91                  |
| 52  | Clear cell              | 1     | 38             | 4              |                           | 2,000      | L colon, spleen, distal pancreatectomy, diaphragm, body wall       | 19          |                     |
| 68  | Clear cell              | 3     | 7              | 8              | Yes                       |            | Splenectomy, Lt colectomy  | 11          |                     |
| 60  | Papillary               | 2     | 21             | 2              |                           | 1,500      | Lt colon mesentary   |             | 71                  |
| 47  | Clear cell              | 2     | 34             | 4              |                           |            | Adrenal  | 57          |                     |
| 62  | Papillary (sarcomatoid) | 4     | 6              | 13             |                           | 1,500      | Lt partial colectomy, distal pancreatectomy, splenectomy, lt liver | 17          |                     |
| 48  | Clear cell              | 3     | 17             | 17             | Yes                       | 1,500      | Lobectomy splenic flexure colon resection, portion diaphragm       | 14          |                     |
| 50  | Clear cell              | 4     | 34             | 6              | Yes                       | 1,200      | Ileum, rt colon, partial resection of inferior vena cava           | 10          |                     |
| 61  | Clear cell              | 2     | 97             | 2.5            | Yes                       | 1,500      |  | 1           |                     |
| 41  | Collecting duct         | 4     | 12             | 8              | Yes                       | 1,200      | Adrenal, significant portion of psoas                              | 15          |                     |
| 47  | Clear cell              | 1     | 180            | 8              |                           | 1,600      |  |             | 56                  |
| 58  | Papillary (sarcomatoid) | 4     | 5              | 4              |                           | 1,500      |  | 12          |                     |
| 58  | Clear cell              | 3     | 67             | 2.5            |                           |            |  |             | 14                  |

some patients did not receive intraoperative radiation therapy, but all patients<sup>8</sup> since 1999 did receive IORT. The mean size of the tumor was 7.4 cm (median 8, range 2 to 17) and 4.5 cm (median 4, range 2 to 8) for patients receiving and not receiving IORT, respectively. Two patients developed local fossa re-recurrences, both of whom received IORT.

Mean followup for the total cohort was 34 months. 9 of the 14 patients died of disease after surgery and had a mean survival of  $17 \pm 16$  months (median 14, range 1 to 57) vs the survivors who had a mean followup of  $66 \pm 34$  months (median 71, range 14 to 86) (fig. 1). All deaths were cancer related. 6 of 10 patients (60%) who received intraoperative radiation therapy and surgery died compared with 3 of 4 (75%) of patients who had surgery alone. There appeared to be no difference in survival due to IORT (fig. 2).

#### DISCUSSION

Isolated fossa recurrence after radical nephrectomy is uncommon and is thought to convey an unfavorable prognosis. Patients have a dismal outcome with observation alone. deKernion et al compared survival of patients with metastatic renal cell carcinoma with no local recurrence to those who had a recurrence within the renal fossa and found that 86% with local recurrence died within 1 year compared with a 40% survival rate with metastases and no local recurrence.<sup>10</sup>

Although it has been 33 years since Skinner et al published on extensive surgery prolonging survival in the setting of isolated local fossa recurrences, there are still relatively few published series of treatment for local recurrence of kidney cancer (table 2). Most of the series reported in the last 2 decades include patients with other renal malignancies, such as spindle cell carcinoma or transitional cell carcinoma, which have different biological behaviors than RCC, as well as including patients who have been previously treated for distant metastatic disease. This heterogeneity in reporting makes interpretation of the literature difficult. The present series does contain a well characterized homogenous population of patients with pure local recurrence of renal cell carcinoma. Additionally, the usefulness of a single mode of adjuvant therapy, IORT, was examined.

There are multiple areas of agreement in the published series, as well as the present series. First the tumor stage at initial radical nephrectomy can vary widely. The series reported by Schrödter et al,<sup>9</sup> Itano et al<sup>6</sup> and Gogus et al<sup>11</sup> contain a substantial number of T1 cases and even low risk T1 cases are reported to develop local recurrence. This un-

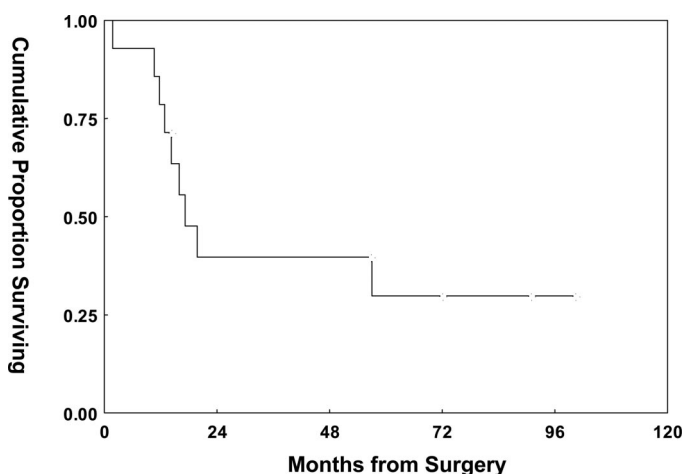


FIG. 1. Kaplan-Meier Curve showing patient survival after resection for local recurrence of RCC. Time in years since surgery is shown on x-axis and cumulative survival percentage is shown on y-axis. Of 14 patients 9 died at median interval of 17 months following surgery.

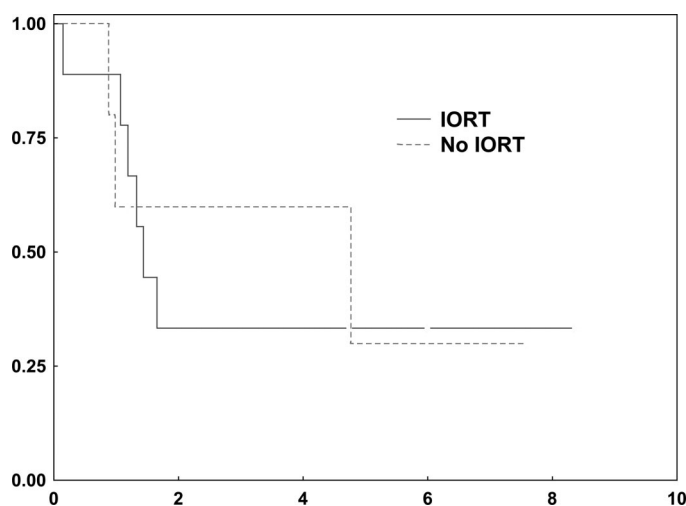


FIG. 2. Kaplan-Meier Curve showing patient survival stratified by those who received intraoperative radiation therapy (solid line) vs those who did not (broken line). Time in years since surgery is shown on x-axis and cumulative survival percentage is shown on y-axis. There appears to be no difference in cohort outcome.

derscores the need for meticulous and careful surgical technique at the time of initial nephrectomy to minimize the risk of local recurrence. Similarly, local recurrence has been reported with all histological subtypes, as well as with all Fuhrman grades of tumor. In summary, there is clearly great biological heterogeneity of tumor behavior in the ability to colonize the renal fossa bed and the current method of assigning risk does not serve to capture this heterogeneity. It is possible that novel molecular markers such as the matrix metalloproteinases<sup>12</sup> and other markers of tissue invasion by penetration, as opposed to metastatic spread by lymphovascular migration might enable patients to be better risk stratified.

The length of time from radical nephrectomy to local recurrence indicates that patients with late local recurrences tend to have better survival, perhaps indicating that a tumor with indolent growth pattern can be well treated with surgical therapy and be unlikely to metastasize. However, no study, including the present study, has shown a statistically significant difference in the interval, although there is a trend to statistical significance in each of the recent studies ( $p = \sim 0.06$ ). Similarly, there is good agreement in between Schrödter et al, Itano et al and the current study that adjuvant therapy does not appear to increase survival, although each study has relatively few patients in each arm. Only Itano et al and our study report 5-year survival data which is similar at 28 and 30%, respectively. Interestingly, the data for patients with a distant metastatic RCC lesion shows a stronger link between the disease-free interval from initial nephrectomy and survival. Kavolius et al from Memorial Sloan-Kettering studied a cohort of 278 with metastatic disease following nephrectomy. Patients undergoing metastectomy with a disease-free interval of greater than 12 months had a 55% overall survival compared with a 9% overall survival of patients who had a disease-free interval of less than 12 months, which was highly statistically significant.<sup>13</sup>

It should be emphasized that this study comprises a selected group of well selected patients. Not all patients who request surgical therapy for massive local recurrence are offered an operation. Other reasonable management options for these patients include radiation therapy and/or systemic therapy. Minimally invasive surgical approaches using laparoscopy have been used.<sup>14</sup> Other novel forms of therapy include ablation via radio frequency or thermal ablation,<sup>15,16</sup> both of which have been used in the setting of local recur-

TABLE 2. Literature review of series of isolated local recurrences of kidney cancers

|                      | Esrig et al <sup>8</sup> | Tanguay et al <sup>20</sup> | Itano et al <sup>6</sup> | Schrödter et al <sup>9</sup> | Gogus et al <sup>11</sup> | Current Study |
|----------------------|--------------------------|-----------------------------|--------------------------|------------------------------|---------------------------|---------------|
| Yrs pt accrual       | 1973–1990                | 1983–1994                   | 1970–1998                | 1991–2000                    | 1994–2002                 | 1990–2003     |
| No. pts              | 11                       | 16                          | 30                       | 16                           | 10                        | 14            |
| Male                 | 10                       |                             | 18                       | 10                           | 7                         | 10            |
| Female               | 1                        |                             | 12                       | 6                            | 3                         | 4             |
| % Symptomatic        | 73                       | 38                          | 60                       | 15                           | 30                        | 7             |
| Mean age (range)     | 59 (41–73)               | 53 (23–74)                  | 67 (35–85)               | 59 (48–69)                   | 51 (26–74)                | 51 (16–68)    |
| Mos to recurrence    | 31                       | 16.5                        | 33.6                     | 45.4                         | 33.6                      | 40            |
| Mean tumor size (cm) |                          |                             |                          | 5.92                         | 8.45                      | 6.35          |
| Survival:            |                          |                             |                          |                              |                           |               |
| 1 Yr                 | 55                       |                             |                          |                              |                           | 86            |
| 3 Yrs                | 36                       |                             | 40                       | 56                           |                           | 40            |
| 5 Yrs                |                          |                             | 28                       |                              |                           | 30            |
| % Mortality          | 18                       | 0                           | 0                        | 0                            | 10                        | 0             |
| % Morbidity          | 18                       | 31                          | 33                       | 0                            | 0                         | 42            |

Most although not all of the reported pathology was renal cell carcinoma. Some patients had been previously treated for other metastatic deposits of RCC. Similar times to develop local recurrence are noted. Also similar mass sizes are present in multiple series. Complication rates vary but mortality is present in older and new series.

rence of RCC, and have the capability to reduce surgical morbidity. The value of these novel techniques in achieving durable local control needs to be examined.

It is intriguing that in this series 3 of 4 female patients are alive vs 2 of 10 of the males. No biological mechanism has been elucidated to explain this observation, but previous authors have hypothesized that there may be some estrogen mediated effect on recurrent RCC.<sup>17</sup> Other series on locally recurrent RCC do not contain this information, making it hard to generalize from the clinical observation in this series.

There are several limitations to the present study. Most importantly, it is a highly selected patient population. We do not have a record of those patients who underwent systemic therapy only for pure locally recurrent RCC. However, while it is possible that patients who received systemic treatment alone may have had equivalent survival rates, most series show a 10% to 20% response rate. To the best of our knowledge, no study has examined the use of systemic therapy for locally recurrent RCC. Secondly, IORT was not administered to all patients in this series, and formal statistical subset analysis is not possible with the few patients in each group. Although both patients who had a second recurrence in the fossa had IORT, it is possible that this is due to the large tumor size in this subgroup (7.5 vs 4.5 cm). Additional post-operative external beam radiation therapy (EBRT) may be needed for patients with large recurrent local renal fossa tumors. Corollary data are observed in the treatment of retroperitoneal sarcomas. The National Cancer Institute performed a randomized trial comparing EBRT alone vs IORT plus EBRT for retroperitoneal sarcomas. Although there was no difference in survival with the addition of IORT, there was an improvement in local control from 20% to 60% with the addition of IORT.<sup>18</sup> A potential improvement in local control would be likely to improve quality of life in this patient group. Although the current study does not show a survival advantage with IORT, because the majority of patients in this study (10 of 14) did have IORT, we believe IORT should be included in the management of renal cell recurrences. Finally, of note, it is interesting to realize that the total number of aggregate patients in these published series is less than 100 worldwide. Results from these retrospective case series are serving as the means for management guidelines for this challenging problem. A prospective, multi-institutional trial or registry will likely be required to effectively answer the question of whether patients do benefit by intervention, especially with multimodal therapy. In the absence of a prospective trial, only patients with good performance status who are free of distant metastatic disease by cross-sectional imaging of the chest, abdomen and pelvis and bone scans, should be offered a change for surgical curative therapy. At present positron emission tomography scans offer limited usefulness with a sensitivity of only 64%.<sup>19</sup>

## CONCLUSIONS

It appears possible that a significant fraction (30%) of a selected group of motivated patients with isolated local recurrence in the renal fossa have durable results at 5-year followup with surgical resection and possibly adjuvant radiation therapy. This can be accomplished with an acceptable low complication rate. IORT does not provide a survival advantage, but the current study is under powered to show a survival advantage.

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#### EDITORIAL COMMENT

The authors report a 13-year experience with 14 patients who underwent a surgical resection of an isolated renal fossa local recurrence. Interestingly, in this current series only 1 patient was symp-

tomatic from the recurrence with the other 13 detected by followup imaging. Ten patients also received intraoperative radiation therapy although no clear therapeutic effect of the added treatment could be observed. The principle histological variant was the conventional clear cell carcinoma (in 8) or high grade/sarcomatoid variant of papillary carcinoma (in 5) or the poor prognostic collecting duct (in 1). Despite extensive surgical resection, involving adjacent organs (8) and perioperative complications in 42% of patients, diffuse metastatic disease developed in 9 of 14 patients after a mean of 17 months. Five patients are alive at the time of the report (14 to 86 months) but they too remain at risk for metastatic disease.

This series, as well as the others mentioned in this report, presents the difficult issue of isolated local recurrence with clarity. This uncommon event for all intents and purposes is a clinical marker for impending metastatic disease. Survival after surgical resection can be equally attributed to disease natural history rather than a surgical intervention. The urological oncologist should do an extensive metastatic evaluation before operation and the potential adverse outcomes should be described. Operations are morbid and extensive, and significant complications are to be expected. Current cytokine based systemic therapies, external beam irradiation, or IORT techniques are ineffective in eradicating the local recurrence as well as preventing metastatic progression. The exciting and ongoing development of novel treatment approaches to advanced renal cancer, such as those agents that target vascular endothelial growth factor, may allow for the development of effective salvage surgical strategies similar to those used effectively today in testicular cancer, such that surgical resection of a local fossa recurrence, as well as other sites of metastatic disease, will be a durable therapeutic event.

*Paul Russo  
Department of Urology  
Memorial Sloan-Kettering Cancer Center  
New York, New York*