Patient Survival After Surgery for Osseous Metastases from Renal Cell Carcinoma*

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Background: Skeletal metastases from renal cell carcinoma are highly destructive vascular lesions. They pose unique surgical challenges due to the risk of life-threatening hemorrhage and resistance to other treatments. The goal of this retrospective study was to evaluate factors that may affect survival after surgical treatment of metastases of renal cell carcinoma.

Methods: We performed a retrospective review of a series of 295 consecutive patients who had been treated for metastatic renal cell carcinoma at one institution between 1974 and 2004. There were 226 men and sixty-nine women. A total of 368 metastases of renal cell tumors to the extremities and pelvis were treated. The surgical procedures included curettage with cementing and/or internal fixation (214 tumors), en bloc resection (117), closed nailing (twenty-seven), amputation (four), and other measures (six). Overall survival was calculated with Kaplan-Meier analysis. The log-rank test was used to evaluate the effect of different variables on overall survival.

Results: The overall patient survival rates at one and five years were 47% and 11%, respectively. The metastatic pattern had a significant effect on the survival rate ($p < 0.0001$): patients with a solitary bone metastasis had the most favorable overall survival rate. Patients with multiple bone-only metastases had a better survival rate than patients with pulmonary metastases ($p = 0.009$). A clear-cell histological subtype was also associated with better survival ($p < 0.0001$). The tumor grade did not predict survival ($p = 0.17$). Fifteen patients (5%) died within four weeks after surgery. The causes included acute pulmonary failure (seven patients), multiorgan failure (six), cerebrovascular accident (one), and hypercalcemia (one). There were no deaths attributable to intraoperative hemorrhage.

Discussion: Survival beyond twelve months is possible for a substantial proportion of patients with metastatic renal cell carcinoma. Patients with a clear-cell histological subtype, bone-only metastases, and a solitary metastasis have superior survival rates. The presence of pulmonary metastases does not predict early death in a reliable manner, and some patients may survive for years with pulmonary and systemic disease. The data are important for surgeons to consider when choosing treatment for these patients. For example, local control of disease and implant stability are important issues for patients with a potential for a long duration of survival.

Level of Evidence: Prognostic Level II. See Instructions to Authors for a complete description of levels of evidence.

Osseous metastases from renal cell carcinoma are difficult to manage[1-3]. They tend to be large, highly destructive, hypervascular tumors. The optimal form of treatment has not been well-established. Conservative operations such as closed nailing may provide temporary stabilization, but they are susceptible to failure secondary to local tumor progression since the disease does not respond reliably to conventional chemotherapy and radiation (Fig. 1)[4-7].

The projected duration of survival of patients is an important factor affecting the decision regarding management of osseous metastases. Patients predicted to have a prolonged survival, such as those with a solitary metastasis, need a du-

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rable construct. Patients anticipated to have a short survival may need only temporary stabilization. Patients who are moribund may not be surgical candidates at all. Unfortunately, with the conventional staging system of the American Joint Commission on Cancer, patients with skeletal metastases are grouped together as having stage-IV disease[8], and there is no accepted method of stratifying patients with regard to the indications for surgical treatment[9,10].

We retrospectively analyzed a consecutive series of patients with metastatic renal cell carcinoma of the appendicular skeleton treated with surgery. The goal was to document the survival of this cohort of patients and to determine clinicopathologic factors that affect survival.

Materials and Methods

Study Design

We performed a retrospective review of a series in patients who had been treated surgically for metastatic renal cell carcinoma involving the pelvis and extremities at the M.D. Anderson Cancer Center in Houston, Texas, between 1974 and 2004. The patients were identified through the orthopaedic oncology surgical database and institutional tumor registry. Medical records, radiographic studies, operative notes, anesthetic records, and pathology reports were reviewed. The study was approved by and performed in accordance with the guidelines of the institutional review board.

We gathered information on demographic characteristics, the site(s) of the metastasis, the stage of the disease, the presence of other metastatic disease, the type of surgery, preoperative embolization, blood loss, blood replacement, the dose of radiation, administration of systemic treatment, recurrence of disease, and complications.

The histological subtype and Fuhrman grade were determined from the pathology reports. The Fuhrman classification assigns nuclear grades of 1 through 4 in increasing order of nuclear size, nuclear irregularity, and nucleolar prominence[11]. Grade 1 indicates round nuclei of approximately 10 μm with no clearly visible nucleoli. Grade 2 indicates nuclei of 15 μm with a somewhat irregular outline, and nucleoli visible at 400× magnification. Grade 3 indicates nuclei of 20 μm with an obviously irregular outline, and nucleoli visible at 100× magnification. Grade-4 nuclei possess the characteristics of grade-3 nuclei, but they are also distinguished by bizarre multilobed shapes, chromatin clumps, and sometimes the

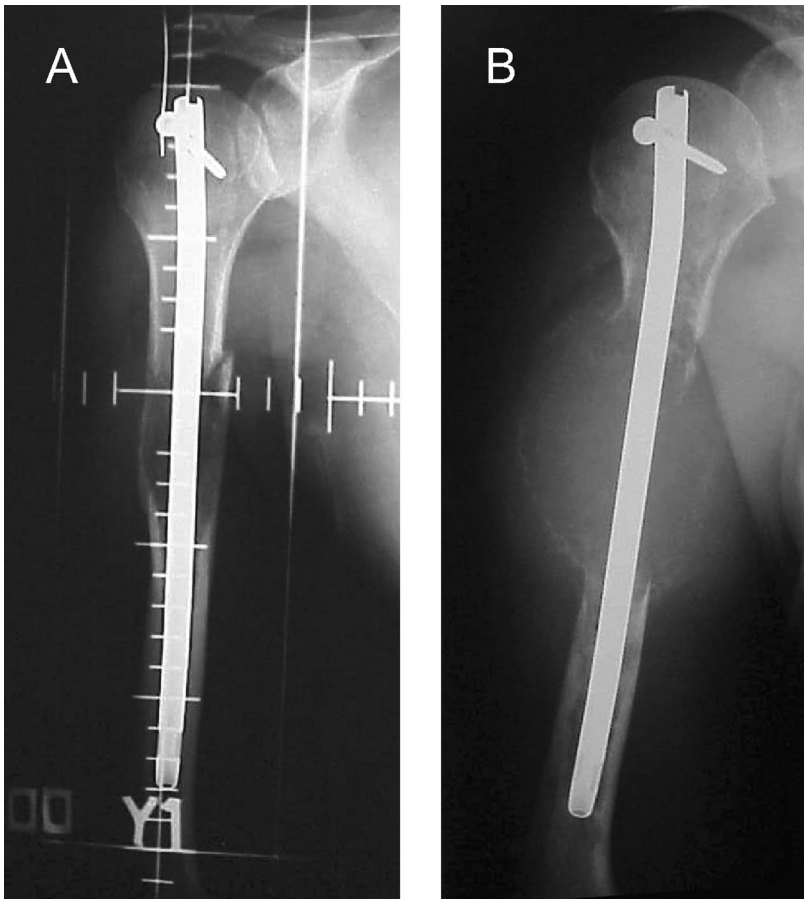

Fig. 1

This patient was referred for treatment after closed nail fixation of a pathologic humeral shaft fracture. Postoperative radiation of 30 Gy was administered. The simulation radiograph is shown (A). Six months later, the patient presented with a massive recurrence at the fracture site (B). The patient was treated with en bloc resection and intercalary prosthetic replacement.

TABLE I Demographics

Gender	
Male	226
Female	69
Age *(yr)*	
Mean	58
Range	26-82
Duration of follow-up *(mo)*	
Median	10
Range	0-163
Sites	368
Upper extremity	140
Clavicle	4
Scapula	9
Humerus	113
Forearm	8
Hand	6
Lower extremity	228
Pelvis	30
Femur	173
Tibia	19
Foot	6

presence of spindle cells. Since the Fuhrman grade was not described until 1982, it did not become widely accepted and utilized until the late 1980s. One hundred and seventy-seven patients had a Fuhrman grade assigned to the primary tumor in the pathology report on the initial biopsy results or on the results of the analysis of the resection specimen obtained at the nephrectomy.

The date and cause of death were determined from information provided by the institutional Department of Tumor Registry (available on patient charts), and this was corroborated by the Social Security Death Index. Radiographs were reviewed for the presence of fracture, extent of local bone destruction, recurrence, failure of the implant, and long-term stability of endoprostheses.

The stage of the disease at the time of surgery was determined by a review of the charts. Particular attention was directed toward chest radiographs, skeletal radiographs, bone scans, magnetic resonance imaging scans, and computed axial tomography scans to document the presence of other metastases. The findings of physical examinations, pathology reports, and operative notes were also reviewed to determine the presence of lymph node metastases and visceral metastases.

Patients

A total of 295 consecutive patients were included in the study. Patient demographics and follow-up data are shown in Table I. For inclusion in this study, patients had to have undergone surgery for metastatic renal cell carcinoma lesion(s) affecting the appendicular skeleton at our institution. Exclusion criteria included treatment solely with nonoperative measures, metastatic disease confined to the cranium or spine, surgery for a metastasis at another institution, or inadequate follow-up (less than twenty-four months, unless the patient died before that time).

The mean duration of follow-up was nineteen months (median, ten months; range, zero to 163 months). One hundred and fifty patients died of disease-related causes twelve months or less after the operation. An additional forty-three patients died between twelve and twenty-four months postoperatively. At the time of the last follow-up, forty-eight patients were still alive. Nine of them had been lost to follow-up. Data were complete for all other patients.

Surgery

There were 368 de novo metastatic tumors (index cases) and twenty-nine cases of locally recurrent metastatic disease. One hundred and sixty-three of the de novo metastases involved a pathologic fracture, and 205 involved an impending fracture. Fifty-two patients (18%) had more than one site of surgery. Forty of these patients had two separate operative sites, and the remaining twelve patients had three to seven operative sites.

Seven attending surgeons performed the operations during the period of the study. The surgical treatment was chosen by the surgeon and was predicated on the patient's health status, the anatomic site of the disease, the local extent of the lesion, and projected patient survival. The type of surgery performed for the index cases is shown in Table II. The surgery included tumor excision in 335 index cases and did not include tumor excision in thirty-three.

Tumor excision was performed with curettage, en bloc resection, or amputation. Curettage was generally performed prior to internal fixation with an intramedullary nail, a long-stem prosthesis, a plate, or another device. A meticulous, aggressive curettage was performed typically to remove all gross tumor. Surgical adjuvants were employed in eighteen cases (5%), at the surgeon's discretion, and included intracavitary argon beam coagulation (ten), liquid nitrogen (four), phenol (three), and hydrogen peroxide (one). The cavities were filled with polymethylmethacrylate in 212 cases (99%) after curettage. The indications for en bloc re-

TABLE II Types of Surgery

	No.	%
Tumor not excised	33	9
Closed nailing	27	7.3
Resection arthroplasty	4	1.1
Other	2	0.5
Tumor excised	335	91
Amputation	4	1.1
En bloc resection	117	31.8
Curettage with or without internal fixation	214	58.1

TABLE III Kaplan-Meier Analysis of Overall Survival

Factor/Subgroup	No. of Patients	Overall Survival at 1 Yr	Overall Survival at 5 Yr	P Value
Metastatic pattern				<0.0001
Bone only, solitary	48	0.78	0.35	
Bone only, multiple	51	0.58	0.11	
Bone and non-pulmonary	52	0.39	0.08	
Bone and pulmonary	144	0.38	0.08	
Histological subtype				<0.0001
Clear-cell	248	0.51	0.12	
Non-clear-cell	47	0.25	0	
Fuhrman grade				0.17
2	39	0.59	0.10	
3	90	0.54	0.11	
4	48	0.36	0.09	
Gender				0.40
Female	69	0.53	0.14	
Male	226	0.45	0.10	
Age				0.76
≤40 yr	17	0.53	0.07	
41-60 yr	169	0.52	0.12	
>60 yr	109	0.51	0.09	

section included bone destruction that precluded standard internal fixation or joint arthroplasty, a solitary bone metastasis, or a locally recurrent tumor associated with established or impending fixation failure. The indication for amputation was extensive multifocal recurrence of disease (three patients) or the inability to perform limb-sparing reconstruction (one).

Statistical Analysis

Overall survival and local relapse-free survival rates were calculated with Kaplan-Meier analysis with use of the log-rank test to compare different groups. Analysis of variance and the Student t test were used to compare the means of different groups. Statistical calculations were performed with SPSS version 12.0 (SPSS, Chicago, Illinois). Significance was defined as $p \leq 0.05$.

Results

Patient Survival

The overall patient survival rate after the first operation for metastatic bone metastasis was 47% at twelve months, 30% at two years, and 11% at five years. The variables that did not have a significant effect on survival included age, gender, surgeon, and the decade during which the surgery was performed (Table III).

The clear-cell histological subtype, which accounted for 84% of the cases, was associated with more favorable patient survival than other variants ($p < 0.0001$). At one year, the overall survival rate was 51% for the patients with the clear-cell subtype compared with 25% for those with a non-clear-cell subtype. At five years, the overall survival rates were 12% and 0%, respectively. With the numbers studied, there was no difference in survival among the various non-clear-cell subtypes.

The Fuhrman grade of the initial primary renal cell tumor was not predictive of long-term patient survival ($p = 0.17$). At one year, the overall survival rate was worse for patients with grade-4 disease than for those with other grades, but by five years, with the numbers studied, there was no significant difference in overall survival (Table III).

Patients were grouped according to four different modes of metastatic presentation: solitary bone metastasis, multiple osseous metastases without other metastases, osseous metastasis with non-pulmonary metastases only, and osseous metastasis with pulmonary metastases (with or without visceral metastases). The largest group of patients (49%) had pulmonary metastases.

The pattern of skeletal metastasis affected overall survival. Patients with a solitary bone metastasis had a significantly better survival rate than all other groups ($p < 0.0001$), with 78% and 35% survival rates at one and five years after the surgery, respectively (Fig. 2). Patients with bone-only metastases also had a better prognosis than patients with pulmonary metastases ($p = 0.009$).

Only one patient survived for longer than ten years. That patient had a solitary bone metastasis and was still free of disease at the time of writing. Although nineteen patients survived for at least five years, fifteen died of the disease between five and ten years. Three patients survived between five and ten years and were alive at the time of the last follow-up.

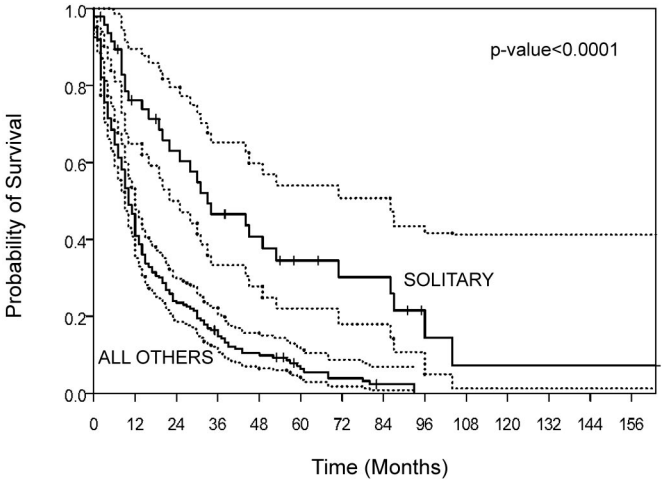

Fig. 2

The overall survival rate of patients with 95% confidence intervals from the time of the first operation for osseous metastases. Patients presenting with an apparently solitary bone lesion had a better survival rate than the patients with other patterns of metastases ($p < 0.0001$). Several patients with pulmonary, with or without other visceral, metastases survived for at least five years. Only one patient with a solitary metastasis survived for longer than ten years.

Fifteen patients survived more than five years but died before ten years.

With the numbers studied, we could not identify a significant difference between en bloc resection and intralesional curettage with regard to survival of patients with a solitary bone metastasis (Fig. 3). Thirty-three patients with a solitary bone metastasis underwent resection, and fifteen patients underwent curettage. The median duration of survival following en bloc resection was forty-five months, and the survival rate was 80% at one year and 38% at five years. The median duration of survival following curettage was twenty-two months, and the survival rate was 73% at one year and 24% at five years.

Fifteen patients (5%) died in the perioperative period (within four weeks after the surgery). The most common cause of death was acute respiratory failure in the presence of pulmonary metastases (seven patients). Rapid progression of visceral disease resulted in multiorgan failure in six patients. Hypercalcemia and a cerebrovascular accident contributed to one death each. Five of the patients who died in the perioperative period had been treated with conservative surgery (no tumor excision). Eight patients treated with curettage of the tumor and internal fixation and two patients who had an en bloc tumor resection died in the perioperative period.

There were no intraoperative or perioperative deaths attributable to massive hemorrhage. The mean intraoperative blood loss was 1123 mL (median, 500 mL; range, 100 to 14,000 mL). The mean intraoperative blood transfusion was 2.2 units of packed red blood cells (median, 1.0 unit; range, zero to thirty units). Twenty cases (5%) involved blood loss of more than 5 L. Selective transcatheter arterial embolization was used prior to surgery in 199 cases (54%). The mean intraoperative blood loss was 1441 mL for patients who underwent embolization compared with 875 mL for those who did not have embolization ($p = 0.002$). The two groups were not randomized, and embolization was used routinely for larger, more central tumors at sites where a tourniquet could not be applied to control intraoperative hemorrhage.

Local Tumor Control

Nineteen patients (6.4%) underwent surgery for local recurrence of disease. The local relapse-free survival rate was 84% at five years. The local relapse-free survival rates at one and five years were 94% and 91% after the 117 en bloc resections and 97% and 74% after the 214 curettage procedures ($p = 0.43$). Within the subset of forty-eight patients with a solitary bone metastasis, we could not demonstrate a significant difference in the local relapse-free survival rate at five years between en bloc resection (thirty-three patients), which was 100%, and curettage (fifteen patients), which was 92% ($p = 0.13$).

Sixteen of the nineteen cases of recurrent disease were controlled with limb-sparing surgery. This consisted of en bloc resection of the involved segment of bone in seven cases, repeat curettage with internal fixation in five, and wide excision of a soft-tissue recurrence in four. Amputation of the extremity was necessary in three patients.

Radiation did not appear to significantly affect the local relapse-free survival rate. For the fifty-seven primary metastatic lesions (20%) for which postoperative radiation was employed, the local relapse-free survival rate at five years was 88%. For the 230 lesions (80%) for which postoperative radiation was not employed, the local relapse-free survival rate at five years was 82% ($p = 0.79$, Fig. 4). However, the two treatment groups were not comparable, and radiation treatment

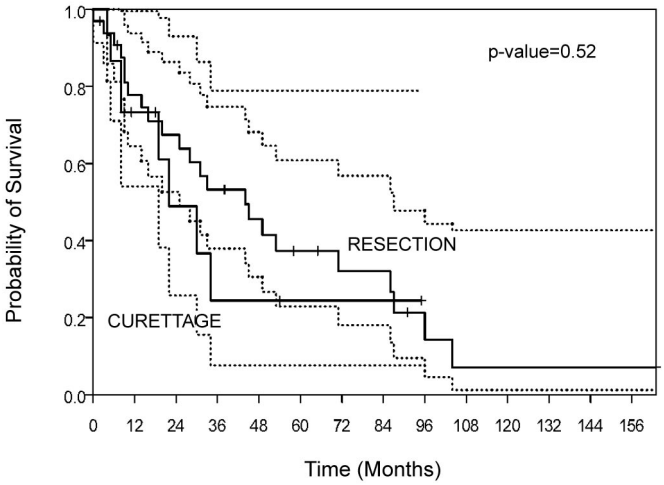

Fig. 3

The effect of resection compared with that of intralesional curettage on the overall survival rate (with 95% confidence intervals) for patients with a solitary bone metastasis ($p = 0.52$).

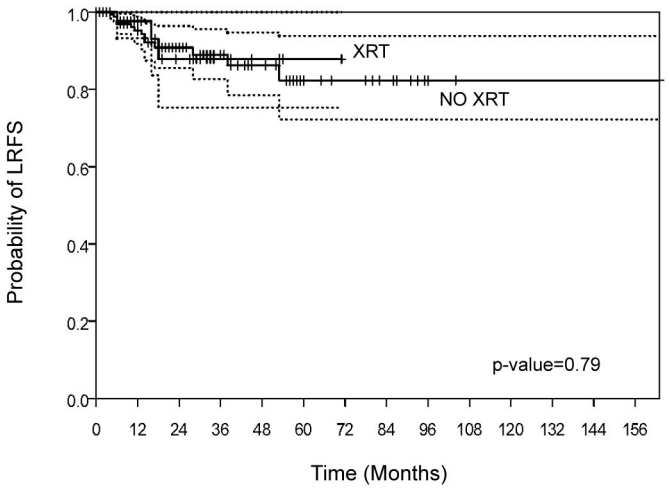

Fig. 4

Postoperative external beam radiation (XRT) did not have a significant effect on the local relapse-free survival rate compared with that of patients who did not receive any radiation (p = 0.79). Patients for whom prior radiation had failed were excluded from the analysis. The 95% confidence intervals are shown. LRFS = local relapse-free survival.

was not randomized. The mean dose of radiation was 30 Gy (a median of ten fractions) with a range of 20 to 40 Gy.

Complications

Perioperative mortality is discussed above in the section on patient survival. Nonfatal perioperative complications included five cases of deep wound infection or necrosis that required a reoperation. One case of infection occurred after closed nail fixation and was treated with surgical irrigation and débridement. A second case of infection occurred after bipolar hip hemiarthroplasty and was also treated with irrigation and débridement. A third case occurred after a proximal humeral resection and endoprosthetic reconstruction. This infection necessitated removal of the implant. Two cases of muscle flap necrosis necessitated surgical débridement.

Other nonfatal perioperative complications included superficial wound necrosis (two cases), pneumonia (three), a retained foreign body (two), symptomatic deep venous thrombosis (two), prosthetic dislocation (two), nerve palsy (two), symptomatic pulmonary embolus (one), fat embolism syndrome (one), upper gastrointestinal bleeding (one), hematoma requiring drainage (one), prolonged ileus (one), and sepsis from an infected central venous catheter (one).

Notable late complications following endoprosthetic replacement included aseptic loosening of the ulnar component of a total elbow replacement in three patients. There were no other cases of aseptic loosening of endoprostheses at other sites. There were no late cases of periprosthetic infection. One patient with a total hip replacement had recurrent dislocations and underwent revision of the acetabular component to a constrained cup. One patient had breakage of an intramedullary femoral nail, but this was associated with a massive local recurrence. There were no instances of nail failure without local recurrence.

Discussion

Survival data for patients with metastatic renal cell carcinoma are relevant to physicians who are confronted with the difficult problem of managing pathologic fractures. The surgeon must consider issues of local control and implant stability for patients who have the potential for extended survival. For patients with a short life expectancy, the surgeon must avoid hastening death through overly aggressive treatment.

Two features of the survival of these patients are notable. First, there is a steep descent in the first year, and many patients die of the disease in the first few months. Second, the death rate diminishes with the passage of time, and a substantial fraction of patients live well beyond one year. Approximately one tenth of the patients survive for more than five years, and prolonged survival is not restricted to patients with a solitary metastasis. Patients with pulmonary and visceral disease may survive for years, and one-quarter of these patients survive at least two years.

The present study identifies several predictors of survival. Patients with a clear-cell histological subtype had a better survival rate than did those with other subtypes. Patients with metastases confined to osseous sites had a better survival rate than did those with metastases in the vital organs. Finally, patients with a solitary bone metastasis had the best survival rate. This finding is consistent with those of previous reports[12-15]. It should be noted that prior to the 1980s, computed tomography scans of the chest, abdomen, and pelvis were not routinely available and some of the patients treated during this time period may not have had a solitary metastasis.

Surprisingly, there were few long-term survivors. Previous authors have reported a relatively high rate of survival (>25%) of patients with a solitary bone metastasis[12,14,16]. We found that, despite an overall survival rate of 35% at five years, there was only one documented survivor beyond ten years. This observation suggests that patients with a solitary bone metastasis have more indolent disease but are not easily cured of the disease.

A variety of treatments were employed in the present study. En bloc resection, which was used in approximately one-third of the cases, was favored for treatment of solitary metastasis, large tumors, periarticular disease, and recurrent tumors. Intralesional excision with curettage, combined with cementing and internal fixation, was performed for most other tumors (58% of the series), particularly small-to-moderately sized diaphyseal tumors. Since this was a retrospective case series, the exact indications for treatment could not always be determined, and they may not have been applied consistently. No meaningful conclusion can be reached by comparing one type of treatment to another under these circumstances. Nevertheless, it is worth noting that, despite the difficulty with performing surgery for these hypervascular tumors, preservation of the limb and local control of disease were achieved in nearly all patients, and the rate of amputation for recurrent, uncontrollable disease was 1%.

It is not feasible, in the framework of the present study, to determine whether curettage of the tumor improved pa-

tient outcome. A small subset of patients (7%) underwent closed nailing without excision of the tumor. These patients had more advanced disease than the patients who underwent curettage and open nailing. Most died in less than a year, and none survived beyond two years. Thus, the group treated with closed nailing could not be compared directly with the group treated with open nailing. The potential benefits of tumor excision with curettage include less intramedullary spread of tumor during nail placement, a greater rigidity of the construct after cementing, reduction of the local tumor mass, and slower progression of the tumor.

It was beyond the scope of this study to examine the other important outcomes of surgery, such as functional results and durability of pain relief. A prospective study is needed to determine if these benefits can be realized consistently and for the duration of a patient's lifetime.

It was not possible to ascribe a survival advantage to en bloc tumor resection over curettage. A previous study demonstrated improved survival of patients who had undergone resection, but there may have been a selection bias toward resection for patients with a solitary metastasis[17]. Another study showed better survival following surgical excision compared with that following no surgery in patients with a solitary metastasis, but en bloc resection resulted in no significant improvement in survival compared with that associated with curettage[13]. With the numbers studied, we also did not find a significant improvement in overall survival after en bloc resection compared with that after curettage in a patient with a solitary metastasis. A retrospective power analysis indicated that the number of evaluable patients in this study provided only a 68% power to detect a difference of twenty-three months in median survival. Despite the lack of statistical justification, we believe en bloc resection remains preferable for treatment of a solitary metastasis because it is the most reliable means of eradicating disease in the extremities and of providing durable control of the disease over a potentially long period of survival. En bloc resection is certainly more attractive when it can be performed with minimal compromise of limb function.

Although some tumors may be responsive to radiation, the effectiveness of postoperative adjuvant radiation is uncertain[18]. In the present study, the lack of a decrease in the rate of local recurrence in the group treated with radiation could be the result of selection bias. The results do not warrant dismissal of postoperative radiation as a viable adjuvant to achieve local tumor control, but they do cause us to question whether radiation can be relied on for local control, particularly after closed nailing. A prospective randomized trial may be necessary to address this question. Likewise, the scope of the current study did not permit analysis of the efficacy of other treatments, such as chemotherapy, bisphosphonates, and radiofrequency ablation[19-23].

An inherent risk of surgery for renal cell metastases to bone is massive intraoperative hemorrhage. Our study suggests that, for most patients, the extent of blood loss is manageable. The mean intraoperative transfusion was two units of packed red blood cells, despite the fact that only one-half of the patients underwent preoperative embolization. The fact that embolization in this series was associated with greater blood loss suggested that there was a strong selection bias toward embolization for more locally advanced tumors. Although not specifically demonstrated in this study, the use of embolization is an accepted practice to reduce blood loss[24].

In summary, approximately one-half of all patients survive for one year after surgery for renal cell metastases, and one-tenth survive for longer than five years. Patients with a clear-cell histological subtype, bone-only metastases, and a solitary metastasis survive longer. The presence of pulmonary metastases does not predict an early death. These data are important to consider when determining the surgical treatment of a particular patient. Local control of disease and implant stability are important issues for a patient with a potential for a long duration of survival. ■

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