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CONTEMPORARY MANAGEMENT OF RENAL CELL CARCINOMA WITH COEXISTENT RENAL ARTERY DISEASE: UPDATE OF THE CLEVELAND CLINIC EXPERIENCE

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ABSTRACT

Objectives. To treat concurrent renal cell carcinoma (RCC) and renal artery disease (RAD), which pose an unusual and challenging management dilemma.

Methods. Before June 1998, 48 patients presented with localized RCC and RAD affecting all the functioning renal parenchyma. These patients were grouped into four distinct categories: group 1, a solitary kidney with RCC and RAD (n = 8); group 2, bilateral RCC and coexistent RAD (n = 9); group 3, unilateral RCC and contralateral RAD (n = 15); and group 4, unilateral RCC and bilateral RAD (n = 16). The most common cause of RAD was atherosclerosis (n = 40), followed by medial fibroplasia (n = 5), renal artery aneurysm (n = 2), and arteriovenous malformation (n = 1).

Results. All patients underwent complete surgical excision of RCC. A nephron-sparing operation was performed preferentially (44 patients), and bilateral renal cancer operations were staged. Eleven patients underwent surgical renal vascular reconstruction in conjunction with either partial (n = 9) or radical (n = 2) nephrectomy. In 2 patients, renal revascularization was accomplished by percutaneous transluminal angioplasty before tumor excision. No perioperative deaths occurred. Postoperatively, preservation of renal function was achieved in 47 patients; 1 patient required chronic dialysis. The overall and cancer-specific 5-year patient survival rates in this series were 66% and 90%, respectively. At a mean follow-up of 58 months, 28 patients were alive with no evidence of malignancy. Six patients died of metastatic RCC, and 14 died of unrelated causes with no evidence of malignancy.

Conclusions. Nephron-sparing surgery combined with selective renal arterial reconstruction can yield gratifying results in this complex patient population. UROLOGY **56:** 382–386, 2000. © 2000, Elsevier Science Inc.

Renal cell carcinoma (RCC) is an uncommon cancer, accounting for only 3% of all malignancies.[1] Renal artery disease (RAD) coexisting in patients with RCC is an even more infrequent clinical presentation that may pose unique and challenging management issues. In patients who have RCC and RAD affecting the same kidney and a normal contralateral kidney, radical nephrectomy is the preferred management. A challenging therapeutic dilemma occurs when all functioning renal parenchyma are affected by both conditions. The deleterious effect on renal function secondary to stenotic lesions in the renal artery is well described.[2,3] Additionally, both invasive and noninvasive imaging modalities have demonstrated the progressive nature of these lesions when left untreated.[4,5] Given the progressive nature, efforts to achieve maximal tumor control must be weighed against the need to preserve renal parenchyma in this complex patient group.

Previously, we reported on the treatment of 34 patients with coexistent RCC and RAD.[6] The results from this initial study suggested that nephron-sparing surgery could be combined with renal arterial reconstruction to achieve long-term preservation of renal function and cancer-specific survival. Since that report, several advances have

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influenced the management of these conditions. Percutaneous approaches are being increasingly used in the treatment of renal artery stenosis and have shown variable results.[7–9] We present our larger experience in the treatment of patients with coexistent RCC and RAD affecting all the functioning renal parenchyma with a longer follow-up of the initially treated patients.

MATERIAL AND METHODS

From January 1969 to June 1998, 48 patients presented with coexistent localized sporadic RCC and RAD affecting all the functioning renal parenchyma. Patients with ipsilateral RCC and RAD and an entirely normal contralateral kidney were excluded from this study. This series included 29 men and 19 women ranging in age from 42 to 85 years (mean age 67). These patients were grouped into four distinct groups: group 1, a solitary kidney with RCC and RAD (n = 8); group 2, bilateral RCC and coexistent RAD (n = 9); group 3, unilateral RCC and contralateral RAD (n = 15); and group 4, unilateral RCC and bilateral RAD (n = 16).

Unilateral RCC was present in 35 patients. Bilateral RCC was present in 13 patients, of whom 9 patients had synchronous and 4 asynchronous presentations. Among the 9 patients with bilateral synchronous RCC, 5 underwent unilateral partial nephrectomy and contralateral radical nephrectomy, and 4 underwent bilateral partial nephrectomy.

RCC was considered to be an incidental finding in patients whose diagnostic evaluation was not initiated by systemic or genitourinary complaints related to the tumor. More patients had incidentally detected RCC (31 patients) than symptomatic tumors (17 patients). Thirty patients presented with findings suggestive of renal artery stenosis, such as hypertension (n = 8) or azotemia (serum creatinine level more than 1.5 mg/dL, n = 16), or both (n = 6). Eighteen patients had no symptoms of either RCC or RAD, and these conditions were discovered incidentally during an evaluation for an unrelated problem.

Patients were evaluated by physical examination, urinalysis, serum creatinine concentration determination, complete blood count, liver function studies, chest radiography, and one or more abdominal imaging studies, such as computed tomography scanning, ultrasonography, magnetic resonance imaging, or arteriography. All patients had angiographically proved RAD. The etiology of RAD was atherosclerosis in 40 patients, medial fibroplasia in 5, renal artery aneurysm in 2, and arteriovenous malformation in 1 patient. The preoperative serum creatinine level was less than 1.5 mg/dL in 20 patients, 1.5 to 2.0 mg/dL in 19 patients, and 2.0 mg/dL or more in 9 patients.

The type of surgical intervention was based on the tumor size and location, technical feasibility of a nephron-sparing cancer operation, specific type and severity of RAD, amount of parenchyma affected by RAD, technical feasibility of surgical revascularization, presence and severity of hypertension, level of overall renal function, and general medical condition of the patient.

All patients in this study had localized and histopathologically proved RCC. Confirmation of negative surgical margins was obtained intraoperatively by frozen section histopathologic examination of the specimen margin.

Pathologic tumor staging was determined according to the most recent tumor, node, and metastasis (TNM) system proposed by the International Union Against Cancer.[10] All tumors were measured during histopathologic examination, and tumor size was reported as the largest dimension of the lesion. In patients with bilateral RCC, the highest stage malignancy in either kidney was used to assign tumor stage.

All patients were followed up at 1, 3, 6, and 12-month intervals and then once yearly for 5 years postoperatively with blood pressure and serum creatinine measurements, chest radiography, excretory urography, and either abdominal ultrasonography or computed tomography. Postoperative clinical data were obtained by review of medical records and, when necessary, by contacting surviving patients or their local physicians. The patient follow-up in this series ranged from 6 to 175 months (mean 58 ± 29).

Two-sample *t* tests were used to compare all mean values. The Pearson chi-square test was used to compare all percentages. Kaplan-Meier survival estimates with log-rank tests were used in all survival data analyses.

RESULTS

All patients underwent complete surgical excision of localized RCC. A nephron-sparing operation was performed in 44 patients; 4 patients underwent radical nephrectomy. The pathologic tumor stage was T1 in 24, T2 in 13, T3a in 5, T3b in 4, and T3c in 2 patients. Thirteen patients underwent renal vascular reconstruction in conjunction with either partial (n = 11) or radical (n = 2) nephrectomy. These procedures were performed on the ipsilateral kidney in 7 patients and on the contralateral kidney in 6 patients. In 2 patients, renal revascularization was accomplished by percutaneous transluminal angioplasty before bilateral partial nephrectomy in the first patient and before ipsilateral partial nephrectomy in the other patient. Surgical renal vascular reconstruction was performed simultaneously in conjunction with partial nephrectomy in 6 patients (five ipsilateral and one contralateral) and in conjunction with contralateral radical nephrectomy in 1 patient. Staged renal vascular reconstruction was performed in the remaining 4 patients after contralateral tumor excision (partial nephrectomy in 3 patients and radical nephrectomy in 1 patient). All revascularizations were technically successful as determined by postoperative isotope renography or arteriography. A variety of surgical techniques were used in this series, including aortorenal bypass (n = 6), splenorenal bypass (n = 4), and hepatorenal bypass (n = 1).

No perioperative deaths occurred in this series. Four patients required temporary dialysis postoperatively for acute renal failure that resolved, including one of the patients who underwent surgical renal revascularization. Postoperatively, preservation of renal function was achieved in 47 of 48 patients. The preoperative serum creatinine level in these patients ranged from 0.8 to 3.1 mg/dL (mean 1.6); the postoperative level ranged from 0.8 to 4.4 mg/dL (mean 1.9). Postoperative blood pressure control was improved in all 8 patients who underwent renal revascularization for hypertension. None of the remaining patients had significant hypertension.

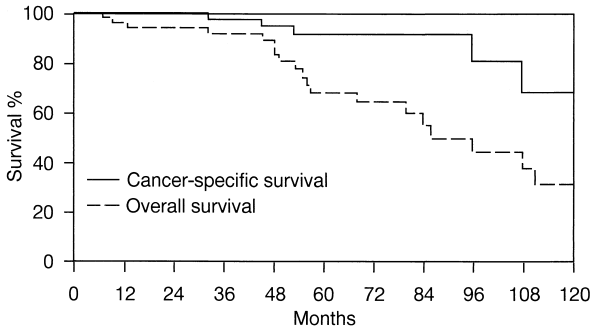

FIGURE 1. *Overall and cancer-specific survival for patients with RCC coexisting with RAD.*

A total of 6 patients (12.5%) developed recurrent RCC. Recurrent malignancy was initially detected locally after nephron-sparing surgery in the remaining portion of the operated kidney in 2 patients (4.5%). In 4 patients (8%), recurrent malignancy was manifested by the detection of one or more metastatic lesions without local recurrence. The overall and cancer-specific actuarial 5-year patient survival rates in this series were 66% and 90%, respectively (median survival time 12.8 years) (Fig. 1). All 6 patients who had recurrent RCC eventually died of metastatic disease. Of the remaining patients, at last follow-up, 28 were alive and tumor free and 14 had died of unrelated causes with no evidence of malignancy at the time of death (6 patients of myocardial infarction, 3 patients of cerebrovascular stroke, 2 patients of chronic obstructive pulmonary disease and respiratory failure, 1 of sepsis, and 3 of unknown causes).

Group 1 (Solitary Kidney with RCC and RAD). Eight patients presented with RCC and RAD affecting an anatomically solitary kidney. One patient who had severe atherosclerotic renal artery stenosis also underwent simultaneous surgical renal revascularization to control hypertension and preserve renal function. A second patient had aneurysmal dilation in two segmental arteries within the kidney, which was thus technically not reconstructible. Atherosclerotic renal artery stenosis was only mildly or moderately severe in the remaining 6 patients and thus was not treated.

Group 2 (Bilateral RCC and Coexistent RAD). A total of 9 patients presented with bilateral synchronous RCC and either unilateral (n = 6) or bilateral (n = 3) RAD. Bilateral renal operations were staged in all of these patients. Two patients who had atherosclerotic renal artery stenosis involving the main renal artery underwent percutaneous transluminal angioplasty before tumor excision. No patient in this group underwent surgical renal revascularization.

Group 3 (Unilateral RCC and Contralateral RAD). A total of 15 patients presented with unilateral RCC and contralateral RAD. Surgical renal revascularization was performed in 3 patients with high-grade left renal artery stenosis. In 2 patients, aortorenal and splenorenal bypass procedures were performed immediately after contralateral radical and partial nephrectomy, respectively. One patient underwent left renal artery reconstruction during aortic replacement followed by staged right partial nephrectomy.

Group 4 (Unilateral RCC and Bilateral RAD). A total of 16 patients presented with unilateral RCC and bilateral RAD. One patient underwent simultaneous radical nephrectomy and contralateral surgical renal vascularization. Five patients underwent simultaneous partial nephrectomy and surgical renal revascularization of the contralateral (n = 1) or ipsilateral (n = 4) kidney. One patient underwent staged partial nephrectomy and contralateral surgical renal revascularization. Postoperative renal function was preserved in 15 patients. One patient had progressive renal insufficiency for several months postoperatively and was maintained on chronic hemodialysis. This patient had a preoperative serum creatinine level of 3.1 mg/dL and underwent excision of two thirds of one kidney. Despite a technically satisfactory splenorenal bypass, progressive renal failure developed from advanced nephrosclerosis.

COMMENT

RCC and RAD occurring concomitantly in the same patient is an unusual clinical presentation. Moreover, when these two conditions affect all the functioning renal parenchyma, management approaches pose a challenging dilemma. A review of published reports shows relatively few data regarding the treatment of patients with these entities. Before 1993, few reports described management of this type of problem.[11–14] These studies reviewed patients who had renal artery stenosis in addition to a variety of pathologic conditions involving the kidney, adrenal glands, or retroperitoneum. In a previous study from our institution, we outlined the treatment approaches in 34 patients with RCC and RAD and proposed treatment strategies for patients with this unusual clinical condition.[6] Specifically, the treatment aims, which include complete tumor excision, renal function preservation, and treatment of associated hypertension, must be weighed before any surgical intervention. No single approach can be uniformly applied to these patients, and treatment must be individualized, taking into account all the aforementioned considerations.

In most patients with RCC and RAD, it is appro-

priate to consider the use of nephron-sparing surgery on the basis of a solitary kidney, bilateral synchronous tumors, contralateral renal involvement with significant RAD, or concurrent renal insufficiency. These are accepted absolute indications for conservative surgery in the treatment of localized RCC, and several studies have reported excellent clinical results with this approach.[15,16] In the current series, nephron-sparing excision of RCC was performed in 44 of 48 patients for one of the aforementioned reasons.

Interestingly, of the 14 patients added to this review, renal tumors were detected incidentally in 13 (93%); 16 (47%) of the initial 34 patients had signs and symptoms related to RCC. These 14 patients all underwent nephron-sparing surgery; at histopathologic review, the renal tumors were Stage pT1 in 12 cases. All these patients remained tumor free until their last follow-up examination. The long-term durability of nephron-sparing surgery for low-stage RCC is well documented in 485 patients treated at our institution, with a local and systemic recurrence rate of 9%.[17] Data from other investigators also suggest that nephron-sparing surgery provides excellent cancer-free survival and preservation of renal function.[15]

Atherosclerosis was the cause of RAD in 40 (83%) of the 48 patients in this series. Since arteriography is no longer performed routinely during the evaluation of patients with RCC, it is appropriate to emphasize the clinical setting in which atherosclerotic RAD is most likely to be detected. This setting comprises patients with a high index of suspicion for renovascular hypertension and/or ischemic nephropathy.[18]

Symptoms suggestive of renovascular hypertension are rare, yet many clinical scenarios point to the diagnosis: (a) age at presentation: the onset of hypertension before 30 or after 55 years of age (typically fibromuscular dysplasia in those younger than 30 years and atherosclerosis in those older than 55 years); (b) a sudden onset and shorter duration of hypertension; (c) hypertension that is difficult to control with three or more medications and a sudden increase in the severity or difficulty in controlling previously mild or well-controlled hypertension; and (d) accelerated, malignant hypertension, hypertensive crises, hypertension associated with episodes of pulmonary edema, and/or gradual impairment of renal function, especially with evidence of generalized atherosclerotic disease. Signs suggestive of renovascular hypertension are severe hypertension, presence of upper abdominal or epigastric bruit (with systolic and diastolic components), severe hypertensive retinopathy, and evidence of generalized atherosclerosis.

Identifying patients with ischemic nephropathy is essential when selecting patients who need to undergo screening testing. Patients usually present with one of the following clinical scenarios, which should alert the physician to the diagnosis of RAD: (a) patients with acute renal failure precipitated by angiotensin-converting enzyme inhibitor antihypertensive therapy; (b) older patients with azotemia and hypertension; (c) older patients with azotemia and generalized atherosclerosis, typically peripheral, coronary, carotid, and cerebrovascular disease; (d) patients with unexplained azotemia, possibly in the absence of hypertension; and (e) disparity of renal size in an older patient.

Several accurate noninvasive imaging studies are now available to diagnose RAD. These studies have largely supplanted arteriography as the initial screening imaging modality for detecting RAD. They include duplex ultrasound, magnetic resonance angiography, and spiral three-dimensional computed tomography angiography. Isotope renography, with or without captopril, is not a reliable screening test for many patients, such as those with bilateral RAD or azotemia. The clinical clues mentioned previously serve to select the patients who should undergo testing for the possible presence of RAD. Although noninvasive screening techniques are available, angiography with intra-arterial injection of contrast material remains necessary before therapy is undertaken.

The need to perform adjunctive surgical renal revascularization in these patients is determined by the specific type, location, extent, and severity of RAD. As shown by several groups, atherosclerotic renal arterial occlusion with loss of renal function occurs commonly with this disease, particularly when the affected renal artery is involved with high-grade (more than 75%) stenosis.[4,5] Severe associated hypertension comprises an additional indication for surgical renal revascularization when the blood pressure control remains refractory to medical treatment. In the present series, surgical renal revascularization was performed for these indications in 10 patients with atherosclerotic RAD. These patients had ostial atherosclerotic lesions that were not amenable to treatment with percutaneous transluminal angioplasty. Two recently treated patients underwent renal artery angioplasty for non-ostial atherosclerotic renal artery stenosis.

In 8 patients, RAD was secondary to nonatherosclerotic conditions, including medial fibroplasia ($n = 5$), renal artery aneurysm ($n = 2$), and arteriovenous malformation ($n = 1$). Although medial fibroplasia can cause renin-mediated hypertension, it is not thought to pose a significant threat to overall renal function.[4] One patient with medial fibroplasia resulting in severe hypertension from bilateral high-grade stenosis underwent unilateral

revascularization; the remaining 4 patients had mild to moderate degrees of medial fibroplasia and adequately controlled hypertension and thus did not require revascularization. Surgical treatment was also not necessary in 3 patients who had a small asymptomatic renal artery aneurysm or an arteriovenous malformation.

Several recent studies have demonstrated superior results with renal artery stent revascularization compared with balloon angioplasty.[8,9] Tuttle *et al.*[9] observed a technical success rate of 98% with stent placement for ostial lesions. Additionally, improved or stable renal function and improved blood pressure control was achieved in most patients. These data suggest that, at present, in patients with atherosclerotic RAD and RCC affecting opposite kidneys, renal artery stent placement may be an alternative treatment in selected cases. The observations in the present study demonstrated that nephron-sparing surgery combined with selective renal arterial reconstruction can yield gratifying results in this complex patient population.

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