Nephrol Dial Transplant (2004) 19: 2789–2796
doi:10.1093/ndt/gfh458
Advance Access publication 17 August 2004

*Original Article*

Nephrology Dialysis Transplantation

# Renal cell carcinoma co-existent with other renal disease: clinico-pathological features in pre-dialysis patients and those receiving dialysis or renal transplantation

Ramón Peces[1,6], Jorge Martínez-Ara[1], José Luis Miguel[1], Javier Arrieta[3], Olga Costero[1], José Luis Górriz[4], Mari-Luz Picazo[2] and Manuel Fresno[5]

Services of [1]Nephrology and [2]Pathology, Hospital Universitario La Paz, Madrid, [3]Service of Nephrology, Hospital Aránzazu, San Sebastián, [4]Service of Nephrology, Hospital Dr Peset, Valencia, [5]Service of Pathology, Hospital Central de Asturias, Oviedo and [6]Section of Nephrology, Hospital General La Mancha Centro, Alcázar de San Juan, Spain

## Abstract

**Background.** Patients on chronic dialysis are prone to developing acquired cystic kidney disease (ACKD), which may lead to the development of renal cell carcinoma (RCC). The risk factors for the development of RCC so far have not been determined in pre-dialysis patients with co-existent renal disease. The aim of this study was to evaluate the clinico-pathological features of RCC in pre-dialysis patients with associated renal diseases or in those undergoing chronic dialysis and renal transplantation.

**Methods.** We studied 32 kidneys from 31 patients with RCC and associated renal diseases. Of those, 18 kidneys were from 17 patients not on renal replacement therapy (RRT) when diagnosed with RCC; 14 patients received dialysis or dialysis followed by renal transplantation. Several clinico-pathological features were analysed and compared between the two groups.

**Results.** Overall, there was a preponderance of males (75%); nephrosclerosis was the predominant co-existent disease (31%). The median intervals from renal disease to RCC in the dialysis and transplanted groups were significantly longer than in the pre-dialysis group ($15.8 \pm 1.1$ *vs* $2.4 \pm 0.7$ years, $P < 0.0001$). In contrast to pre-dialysis RCC, the dialysis and transplant RCC groups had greater frequency of ACKD (100 *vs* 28%, $P < 0.0001$), papillary type RCC (43 *vs* 11%, $P < 0.05$) and multifocal tumours (43 *vs* 5%, $P < 0.05$). At the end of the study, 71% of dialysis and transplanted patients and 72% of pre-dialysis patients were alive.

**Conclusions.** ACKD develops in dialysis patients, as it does in those with renal disease prior to RRT. The duration of renal disease, rather than the dialysis procedure itself, appears to be the main determinant of ACKD and RCC. The RCC occurring in patients with ACKD and prolonged RRT is more frequently of the papillary type and multifocal than the RCC occurring in patients with no or few acquired cysts and a short history of renal disease. Long-term outcomes did not differ between the two groups.

**Keywords:** acquired cystic kidney disease; haemodialysis; nephrectomy; pre-dialysis; renal cell carcinoma; renal transplantation

*Correspondence and offprint requests to*: Dr R. Peces, Sección de Nefrología, Hospital General La Mancha Centro, Avenida de la Constitución, 3, 13600 Alcázar de San Juan, Ciudad Real, Spain. Email: cpeces@varnet.com

## Introduction

Renal cell carcinoma (RCC) accounts for 2–3% of all adult cancers, and has many unusual features in its presentation, diagnosis and management [1]. The pre-malignant lesions of RCC have not been fully described. Acquired cystic kidney disease (ACKD) is a well-recognized disorder associated with chronic renal failure (CRF) and is accompanied by a high incidence of RCC [2]. To date, the pathogeneses of ACKD and the RCC associated with it remain undetermined. Several factors are considered to contribute to the development of ACKD and RCC in CRF patients: ischaemia, obstruction of renal tubules due to oxalate deposits, uraemia, dialysis-related substances, genetic changes and growth factors [3–6]. Specific RCC variants have distinctive chromosome alterations, and several genes have been implicated in the development of RCC. However, concerning ACKD lesions

as the precursor of RCC, there are no convincing reports of molecular alterations. In addition, depressed immunity due to the use of immunosuppressive agents is considered to cause cancer in transplanted kidneys [3,5,7]. We have reported previously the incidence of RCC in the general population in an area of Spain (Asturias) as 11 in 100 000 persons per year [8]. Also in accord with other studies, we found a prevalence of RCC in haemodialysis and renal transplant patients ~40–100 times greater than in the general population [2,5,7]. However, no study has been done to examine the characteristics of RCC in pre-dialysis patients with co-existent renal diseases, and no study has compared the co-existent pathology in these patients with any that developed after the start of renal replacement therapy (RRT).

We present our findings in 32 instances of RCC from 31 patients with other renal disease who had RCC before or after the start of RRT. Moreover, we attempted to identify significant differences in the clinico-pathological features of RCC in both groups of patients with associated renal disease to account for differences in their biological behaviours. The long-term outcomes of these patients were also analysed.

## Patients and methods

We obtained the following clinical information on any patient with RCC and associated renal disease: sex, age at diagnosis of renal disease, age at diagnosis of RCC, age at onset of end-stage renal disease (ESRD), the presenting features of the renal disease, the underlying lesions, duration of dialysis and transplantation, the reason for diagnosing RCC, the confirmations of diagnosis, renal function at presentation, pathological stage, surgical outcome and the type of treatment received.

We studied a total of 32 kidneys with RCC and other co-existent renal diseases from 31 patients at four medical centres. Two of the specimens were from one patient who had both kidneys removed at nephrectomies performed 29 months apart, pre-dialysis and after dialysis was started. For the purpose of this study, the kidneys and tumours from each of the two operations are given separate case numbers. Eighteen patients were not on RRT at the time RCC was diagnosed, eight were on haemodialysis alone and six patients had haemodialysis followed by renal transplantation. Until tumour development, grafts in four patients had functioned well, but the grafts in two patients did not, and in them haemodialysis had to be resumed. The underlying pathologies were confirmed by ultrasound, computed tomography (CT) and, in some cases, magnetic resonance imaging (MRI) and arteriography. The 32 RCC were histologically proven and graded after nephrectomy (29 patients) or autopsy (two patients). Radical nephrectomy was done on 28 patients and partial nephrectomy on one. The nephrectomies or autopsies were performed between February 1981 and March 2001. All renal specimens were fixed in 10% formalin, and routinely processed for paraffin embedding. Histological sections were cut at 6 μm and were stained with haematoxylin and eosin. For the purpose of this study, all specimens were inspected by two of us (M.L.P. and M.F.). Tumours exhibiting mixed histological patterns were classified according to the predominant pattern. Tumours with papillary structures, regardless of extent, were categorized as papillary RCC. Papillary tumours of <0.5 cm in diameter were labelled renal adenomas. Sarcomatoid change was considered the high grade end of the cytological spectrum of any of the histological patterns observed to contain prominent spindle cell features. The non-tumorous parts of the kidneys were inspected for the presence of other lesions. The histological features of ACKD include markedly dilated cysts, with or without papillary or stratified epithelial projections, and clusters of multiple small cysts lined with faintly eosinophilic cytoplasm. Tumour stage was determined according to the type of tumour and the nodes and metastases system (TNM), and the cellular grade as G1–G4 [1,9]. All patients were evaluated at regular intervals post-operatively with chest X-rays, ultrasound and CT.

Among those who received renal transplants, six patients had haemodialysis. Cyclosporin, prednisone and azathioprine were used for immunosuppression in four patients, cyclosporin and prednisone in one, and cyclosporin, prednisone and mycophenolate mofetil in one.

All data were analysed using the Student *t*-test, $\chi^2$ and Fisher's exact tests. The values are given as means ± SEM. The adopted significance level was $P < 0.05$.

## Results

The overall data and outcomes of the pre-dialysis RCC patients with co-existent renal diseases are presented in Tables 1 and 2. Three patients had mild renal insufficiency at the time of presentation, 10 had mild to moderate renal insufficiency, and five had advanced renal failure. In this group, 11 of the 18 patients ended up on haemodialysis. In cases 1, 2, 4, 9, 10, 17 and 18, radical nephrectomies necessitated immediate post-operative haemodialysis. Case 3 started haemodialysis 3 weeks before nephrectomy. Cases 5, 6 and 7 needed haemodialysis at 5 years, 6 months and 9 months, respectively, after surgery. Cases 8, 15 and 16 remained in stable chronic renal failure. In cases 1, 2 and 18 considered to have anatomically or functionally solitary kidneys, the non-tumorous parts of the kidneys revealed sclerotic glomerular lesions and dysplastic tubular epithelium adjacent to RCC. There were signs of ACKD in the non-tumorous parts of the kidneys in 5 of 18 cases (28%). All of them had hyperplasia of the cyst wall epithelium. In addition, the pre-operative CT showed multiple cysts in contralateral kidney in those five patients. The incidence of papillary tumour in this group was 11% (2 out of 18). One patient (case 3) died of septicaemia after 6 months on haemodialysis with no evidence of malignancy at death. One patient (case 11) died of a cerebral vascular accident after nephrectomy. Two patients (cases 13 and 14) died of metastatic disease (brain and lung, respectively) at 9 and 2 months, after surgery. Nine patients were alive and free of malignancy for 17–240 months after the start of haemodialysis, one was alive after a resection of an intestinal metastasis and 32 months on haemodialysis, and three remained alive free of malignancy but with

**Table 1.** Clinical data from pre-dialysis patients with RCC and co-existent renal disease

| Case no. | Sex | Age at diagnosis of renal disease (years) | Original renal disease | Presentation of RCC | Age at diagnosis of RCC (years) | Pre-operative serum Cr (mg/dl) | Pre-operative CrCl (ml/min) |
|---|---|---|---|---|---|---|---|
| 1 | M | 54 | Left agenesis | Flank pain | 54 | 1.2 | 63 |
| 2 | M | 59 | Right hydronephrosis | Renal mass | 59 | 1.5 | 56 |
| 3 | F | 72 | Amyloidosis | Renal mass | 72 | 10.8 | 2 |
| 4 | M | 77 | Nephrosclerosis | Renal mass | 78 | 4.3 | 18 |
| 5 | M | 65 | DN | Flank pain | 70 | 2.4 | 38 |
| 6 | M | 34 | FSGS | Renal mass | 35 | 3.2 | 41 |
| 7 | M | 45 | Nephrosclerosis | Renal mass | 48 | 3.1 | 39 |
| 8 | M | 70 | Nephrosclerosis | Renal mass | 76 | 1.7 | 49 |
| 9 | M | 36 | IgA GN | Renal mass | 45 | 6.7 | 12 |
| 10 | M | 37 | CIN | Renal mass | 37 | 7.0 | 10 |
| 11 | M | 72 | Nephrosclerosis | Renal mass | 75 | 2.5 | 22 |
| 12 | F | 65 | FSGS | Flank pain | 65 | 1.9 | 30 |
| 13 | M | 68 | PKD | Haematuria | 68 | 6.5 | 9 |
| 14 | M | 78 | Nephrosclerosis | Haematuria | 78 | 5.5 | 10 |
| 15 | M | 60 | DN | Renal mass | 66 | 1.7 | 40 |
| 16 | F | 58 | DN | Renal mass | 63 | 3.8 | 20 |
| 17 | M | 68 | Nephrosclerosis | Renal mass | 73 | 4.1 | 16 |
| 18 | M | 54 | Left hypoplasia | Renal mass | 54 | 1.3 | 60 |

DN = diabetic nephropathy; FSGS = focal segmental glomerulosclerosis; CIN = chronic interstitial nephropathy; PKD = polycystic kidney disease; Cr = creatinine.

**Table 2.** Pathological and prognostic data from pre-dialysis patients with RCC and co-existent renal disease

| Case no. | Involved kidney | Non-tumorous kidney | Tumour type | Tumour size (cm) | Tumour stage | Cellular grade | Outcome | Follow-up period (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | Right | GS | CCC | 7 × 5 | T1N0M0 | G1 | HD, metastasis | 32 |
| 2 | Left | GS | CCC | 10 × 4 | T2N0M0 | G1 | HD, tumour free | 26 |
| 3 | Right | ACKD | PC | 5.2 × 5 | T1N0M0 | G1 | HD, deceased, tumour free | 6 |
| 4 | Left | ACKD | PC | 8 × 6 | T2N0M0 | G2 | HD, tumour free | 20 |
| 5 | Right | DN | CCC | 21 × 11 | T3N1M0 | G2 | HD, tumour free | 72 |
| 6 | Right | FSGS | CCC | 3 × 2 | T1N0M0 | G2 | HD, tumour free | 24 |
| 7 | Left | ACKD | CCC | 7.5 × 4.5 | T3N0M0 | G4 | HD, tumour free | 48 |
| 8 | Right | GS | CCC | 5.5 × 4.5 | T3N0M0 | G2 | CRF, tumour free | 7 |
| 9 | Right | ACKD | CCC | 5 × 4.5 | T3N0M0 | G2 | HD, tumour free | 66 |
| 10 | Left | ACKD[a] | CCC[b] | 6 × 5 | T3N0M0 | G2 | HD, tumour free | 240 |
| 11 | Right | GS | CCC | 3.5 × 3 | T1N0M0 | G1 | Deceased, CVA | 1 |
| 12 | Right | FSGS | CCC | 5.5 × 4.5 | T3N0M0 | G2 | Deceased, breast cancer | 13 |
| 13 | Left | PKD | CCC | 3.8 × 3.5 | T1N0M0 | G2 | Deceased, metastasis | 9 |
| 14 | Left | GS | CCC | 9 × 8 | T3N1M0 | G2 | Deceased, metastasis | 2 |
| 15 | Right | DN | CCC | 6 × 4.5 | T3N0M0 | G2 | CRF, tumour free | 13 |
| 16 | Right | DN | CCC | 4 × 3.5 | T2N2M0 | G2 | CRF, tumour free | 9 |
| 17 | Right | GS | CCC | 6.5 × 5.5 | T2N0M0 | G2 | HD, tumour free | 17 |
| 18 | Right | GS | CCC | 10.5 × 10 | T3N2M1 | G1 | HD, tumour free | 36 |

GS = glomerular sclerosis; ACKD = acquired cystic kidney disease; PKD = polycystic kidney disease; DN = diabetic nephropathy; FSGS = focal segmental glomerulosclerosis; CCC = clear cell carcinoma; PC = papillary carcinoma; TNM = tumour node metastasis; HD = haemodialysis; CRF = chronic renal failure; CVA = cerebral vascular accident.
[a]Papillary adenomas.
[b]Multifocal.

stable CRF. One patient in this group (case 12), in addition to RCC, presented another type of malignancy (breast carcinoma with metastasis).

The overall data and outcomes for patients with RCC detected in dialysis or after transplantation are presented in Tables 3 and 4. The median interval from the onset of haemodialysis to RCC in males was significantly shorter than in females ($68 \pm 19$ *vs* $189 \pm 29$ months, $P < 0.005$). The native kidneys showed non-specific features of ESRD with extensive tubular atrophy, interstitial fibrosis and arteriosclerosis. In the non-tumorous parts of the kidneys, ACKD was found in all cases. In all of them, there was epithelial hyperplasia of the cyst wall, and four cases had papillary adenomas. In addition, the pre-operative CT showed multiple cysts in the contralateral kidneys of all of them. Six patients were alive on haemodialysis and free of recurrence for 1–211 months after surgery, and three were alive with functioning renal grafts. One patient (case 3) died of cardiac arrest after 24 months on haemodialysis with no evidence of malignancy at death. One patient (case 4) who died had pulmonary metastasis. Two cases of RCC in this group (cases 9 and 10) were categorized as sarcomatoid and they died of causes related to the tumour. Four patients in this group (cases 3, 12, 13 and 9) in addition to RCC had several different types of tumours. Case 3 had had a sigmoid adenocarcinoma 10 years before and case 12 a rectal adenocarcinoma 26 months earlier. Case 13, in addition to RCC (found at autopsy), had a verrucous carcinoma of the larynx 24 months earlier, 2 months earlier had been diagnosed to have a bronchial squamous cell carcinoma with metastasis, and his autopsy revealed an ipsilateral transitional cell carcinoma of the renal pelvis. In case 9, in addition to RCC, a medullary thyroid carcinoma was found at autopsy. Table 5 shows a summary of the clinical and pathological data from the five patients with RCC and other tumours.

Table 6 compares clinical and pathological data from both groups of patients with RCC. There was an overall preponderance of males (75%).

## Discussion

Although the risk of RCC, especially the papillary type, has been reported to be increased in patients with ACKD-associated CRF who are on dialysis, reports of ACKD and RCC developing in CRF without dialysis treatment are limited [10]. In contrast to RCC in non-uraemic patients, RCC patients with ACKD have a high incidence of papillary RCC. Atypical cysts with extensive papillary hyperplasia often are the precursors of papillary renal adenoma and cancer in these patients. Papillary tumours have an incidence of ~50% in non-uraemic patients and account for ~4.8% of renal neoplasms in them [11]. Papillary RCC has a better prognosis than non-papillary RCC, and genetic and molecular analyses reveal that papillary RCC differs from non-papillary RCC [5,11–13]. Whether or

**Table 3.** Clinical data from patients with RCC in dialysis and after renal transplantation

| Case no. | Sex | Age at diagnosis of renal disease (years) | Original renal disease | Age at ESRD (years) | Presentation of RCC | Age at diagnosis of RCC (years) | RRT at diagnosis of RCC (months) |
|---|---|---|---|---|---|---|---|
| 1 | F | 48 | Wegener | 49 | Renal mass | 69 | HD (240) |
| 2 | M | 40 | FSGS | 51 | Renal mass | 52 | HD (14) |
| 3 | M | 50 | Nephrosclerosis | 64 | Renal mass | 72 | HD (88) |
| 4 | M | 45 | Unknown | 59 | Metastasis | 61 | HD (25) |
| 5 | F | 31 | Extracapillary GN | 31 | Renal mass | 40 | HD (114) |
| 6 | F | 28 | IgA GN | 28 | Haematoma | 38 | HD (125) |
| 7 | M | 37 | CIN | 37 | Renal mass | 38 | HD (12) |
| 8 | M | 64 | Nephrosclerosis | 70 | Renal mass | 74 | HD (59) |
| 9 | F | 23 | CIN, reflux | 27 | Flank pain | 44 | HD (48), RT (12), HD (153) |
| 10 | F | 23 | CN | 23 | Renal mass | 54 | HD (24), RT (76), HD (156) |
| 11 | M | 42 | Nephrosclerosis | 52 | Haematuria | 61 | HD (44), RT (72) |
| 12 | M | 60 | CIN, lithiasis | 65 | Renal mass | 73 | HD (40), RT (47) |
| 13 | M | 55 | Nephrosclerosis | 62 | Renal mass | 65 | HD (3), RT (27) |
| 14 | M | 28 | IgA GN | 38 | Renal mass | 54 | HD (9), RT (177) |

FSGS = focal segmental glomerulosclerosis; GN = glomerulonephritis; CIN = chronic interstitial nephropathy; CN = cortical necrosis; RRT = renal replacement therapy; HD = haemodialysis; RT = renal transplantation.

**Table 4.** Pathological and prognostic data from patients with RCC in dialysis and after renal transplantation

| Case no. | Involved kidney | Non tumorous kidney | Tumour type | Tumour size (cm) | Tumour stage | Cellular grade | Outcome | Follow-up period (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | Right | ACKD[a] | PC[b] | 4 × 3.5 | T1N0M0 | G3 | HD, tumour free | 4 |
| 2 | Left | ACKD | PC[b] | 4.5 × 3 | T1N0M0 | G2 | HD, tumour free | 3 |
| 3 | Left | ACKD | CCC | 8 × 7 | T2N0M0 | G2 | HD, deceased, tumour free | 24 |
| 4 | Right | ACKD[a] | CCC | 12 × 6 | T3N0M1 | G2 | HD, deceased, metastasis | 0 |
| 5 | Left | ACKD | CCC | 1.5 × 1.5 | T1N0M0 | G2 | HD, tumour free | 34 |
| 6 | Left | ACKD | CCC | 1.2 × 1.2 | T1N0M0 | G2 | HD, tumour free | 123 |
| 7 | Right | ACKD | CCC | 1.7 × 1.5 | T1N0M0 | G2 | HD, tumour free | 211 |
| 8 | Right | ACKD | PC | 3 × 2 | T3N0M0 | G2 | HD, tumour free | 1 |
| 9 | Left | ACKD[a] | CDC[b] | 5 × 3 | T3N2M0 | G4 | HD, deceased | 1 |
| 10 | Left | ACKD | PC[b] | 14 × 6 | T3N2M1 | G4 | HD, deceased, metastasis | 5 |
| 11 | Right | ACKD | CCC[b] | 5.5 × 5 | T1N1M0 | G2 | RT, tumour free | 16 |
| 12 | Left | ACKD[a] | PC | 2.5 × 2.2 | T1N0M0 | G1 | RT, tumour free | 34 |
| 13 | Left | ACKD | CCC[b] | 3 × 3 | T2N0M0 | G2 | RT, deceased, lung cancer | 0 |
| 14 | Left | ACKD | PC | 3 × 2.5 | T1N0M0 | G1 | RT, tumour free | 3 |

ACKD = acquired cystic kidney disease; FSGS = focal segmental glomerulosclerosis; CCC = clear cell carcinoma; PC = papillary carcinoma; CDC = collecting duct carcinoma; TNM = tumour node metastasis.
[a]Papillary adenomas.
[b]Multifocal.

**Table 5.** Clinical and pathological data from five patients with RCC and other associated tumours

| RCC type | Situation at diagnosis of RCC | Associated carcinomas |
|---|---|---|
| CCC | Pre-dialysis | Breast (concomitant) |
| CCC | HD | Sigmoid (10 years earlier) |
| CDC[a] | HD (previous RT) | Medullary thyroid (concomitant) |
| PC | RT | Rectal (26 months earlier) |
| CCC[a] | RT | Larynx (2 years earlier), bronchial (concomitant), transitional renal pelvis (concomitant) |

CCC = clear cell carcinoma; CDC = collecting duct carcinoma; PC = papillary carcinoma; HD = haemodialysis; RT = renal transplantation.
[a]Multifocal.

**Table 6.** Comparison of clinical and pathological data from both groups of patients with RCC

| Variable | Pre-dialysis RCC patients | Dialysis or transplanted RCC patients | *P* |
|---|---|---|---|
| Sex (M/F) | 15/3 | 9/5 | NS |
| Age at diagnosis of renal disease (years)* | 59.5 ± 3.2 | 41.0 ± 3.5 | < 0.005 |
| Age at diagnosis of RCC (years)* | 62.0 ± 3.2 | 56.7 ± 3.5 | NS |
| Duration of renal disease (years)* | 2.4 ± 0.7 | 15.8 ± 2.1 | < 0.0001 |
| Incidental presentation | 13/18 (72%) | 10/14 (71%) | NS |
| Maximum diameter of the tumour (cm)* | 7.0 ± 0.9 | 5.2 ± 1.0 | NS |
| ACKD frequency | 5/18 (28%) | 14/14 (100%) | < 0.0001 |
| PC frequency | 2/18 (11%) | 6/14 (43%) | < 0.05 |
| Multifocal frequency | 1/18 (5%) | 6/14 (43%) | < 0.05 |
| T3 and T4 frequency | 9/18 (50%) | 4/14 (28%) | NS |
| G3 and G4 frequency | 1/18 (5%) | 3/14 (21%) | NS |
| Overall survival rate | 13/18 (72%) | 10/14 (71%) | NS |
| Follow-up period of survivors (months)* | 39.9 ± 14.2 | 45.3 ± 21.6 | NS |
| Metastasis rate | 3/18 (17%) | 2/14 (14%) | NS |

*Mean ± SEM.
ACKD = acquired cystic kidney disease; PC = papillary carcinoma; NS = not significant.

not clinico-pathological features of RCC in pre-dialysis patients with co-existent renal disease differ from those on dialysis and those of transplanted patients is unclear at present.

Our study provides a clinico-pathological analysis of a large series of patients who developed RCC before or after starting RRT. The pre-dialysis RCC group comprised a wide spectrum of renal diseases with a predominance of nephrosclerosis and diabetic nephropathy. In some cases, considered to have anatomically or functionally solitary kidneys, the non-tumorous parts of the kidneys revealed sclerotic glomerular lesions and dysplastic tubular epithelium adjacent to the RCC. The remaining cases had light-moderate to severe CRF when RCC was diagnosed, and the histology of the non-tumorous parts of their

kidneys revealed variable grades of nephrosclerosis and interstitial fibrosis. On the other hand, only some cases in this group had ACKD, and a low proportion of the cases had papillary RCC or multifocal tumours.

The RCC in dialysis and transplanted patients also represented a wide spectrum of renal diseases, with a predominance of nephrosclerosis and glomerulonephritis. Several cases had a long history of CRF and were on haemodialysis when RCC was diagnosed; other cases also had long histories of CRF, were on haemodialysis and had a renal transplant, and some of the latter had functioning renal grafts when RCC was diagnosed. In this group, males had shorter durations of RRT at their diagnosis of RCC than females. Histological studies on the non-tumorous parts of the kidneys revealed in all 14 of the cases the presence of ACKD (four with adenomas). A high proportion of cases in this group had multifocal renal tumours. In addition, the incidence of papillary tumour in this group was high.

It is difficult to confirm whether or not ACKD and RCC are more common in patients with underlying hypertensive renal disease and nephrosclerosis [14–16]. Further studies are necessary to clarify this issue. Intratubular epithelial dysplasia associated with nephrosclerosis and adjacent to RCC might represent precursor lesions along the spectrum ranging from dysplasia to frank carcinoma [14]. The severe nephrosclerosis of CRF dissects the nephron into unattached tubular and cystic elements that show both atrophic and hyperplastic changes. Hyperplasia seems to represent attempts at regeneration promoted by renotropic substances that have the attributes of growth factors [6]. Normal regeneration is impossible in these diseased kidneys, and the outcomes of attempted growth seem to be ACKD, papillary cystic hyperplasia or renal tumours. Thus, it has been demonstrated that patients with mild CRF in various renal diseases may develop ACKD [17]. Renal cyst development may be a manifestation of tubulointerstitial damage. Whether or not mild and moderate renal impairment cause ACKD and RCC has not yet been determined.

Our findings indicate that dialysis and transplant patients had longer durations of renal disease before developing RCC than pre-dialysis patients. ACKD was a constant finding in dialysis and transplanted patients, and less frequent in pre-dialysis patients. In addition, the incidence of papillary RCC in dialysis and transplanted patients was higher than in pre-dialysis patients. This may represent an aetiological link between ACKD and papillary RCC in dialysis and transplanted patients. Moreover, these findings suggest that different cellular mechanism underlie the development of papillary RCC and non-papillary RCC. The frequency of multifocal RCC in dialysis and transplanted patients also was higher than in pre-dialysis patients. Therefore, despite the similar histological appearances of the tumours, RCC that occurs in patients with ACKD because of long-term RRT may be different from the carcinoma that occurs in patients with no or few acquired cysts and very short histories of renal disease.

As other studies, this study confirms that ACKD is not restricted to patients undergoing RRT, since it also develops in those with chronic renal disease but not on dialysis [10]. Irrespective of the original renal disease, ACKD may predispose to RCC not only in dialysis and transplanted patients, but also in those who have chronic renal disease before the initation of dialysis. However, RCC also develops in patients with co-existent renal disease without ACKD. This suggests a factor that mediates cyst or tumour proliferation, or both, independent of treatment with dialysis or transplantation. The superimposition of depressed immunity due to uraemia on ACKD may accelerate the growth of pre-existing pre-malignant lesions in chronic dialysis patients [12]. Due to the use of inmunosuppressive agents after renal transplantation, the risks of malignancy in the kidney or of the development of other types of tumours would increase [5,18].

In our present study, whereas RCC in the majority of patients without RRT were discovered incidentally during the work-up of renal disease, in dialysis and transplanted patients most tumours were discovered through ultrasound screening for ACKD. This finding indicates that the tumours might exist for long periods before clinical expression. The increasing use of imaging procedures to detect pre-symptomatic tumours may be contributing to the rapidly increasing incidence of RCC [8,19,20].

It has been reported that the prognosis for dialysis patients with RCC may be better than that for non-uraemic patients with RCC because of the low rate of metastasis in them [2]. In our study, tumour size, the frequency of an RCC with an advanced clinical stage and metastasis rate were not different between the two groups.

In summary, ACKD develops not only in dialysis patients, but also in those with co-existent renal disease before initiation of RRT. ACKD in patients with chronic renal disease before and after the introduction of RRT may predispose to RCC. The duration of renal disease, rather than the dialysis procedure itself, appears to be the main determinant of ACKD and RCC. RCC that occurs in patients with ACKD and long RRT is more frequently of the papillary type and multifocal than RCC that occurs in patients with no or few acquired cysts and a rather short history of renal disease. Long-term outcomes did not differ between the two groups. Regular screening of patients with chronic renal disease may contribute to an increase the detection of pre-symptomatic tumours, allowing earlier treatment.

*Acknowledgements.* The authors thank the following physicians for allowing us to study their patients: Dr J. Guederiaga (Hospital San Agustín, Avilés, Asturias) and Dr M. Baños (Hospital Cabueñes, Gijón, Asturias).

*Conflict of interest statement.* None declared.

## References


1. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med* 1996; 335: 865–875
2. Ishikawa I. Uremic acquired renal cystic disease: natural history and complications. *Nephron* 1991; 58: 257–267
3. Levine LA, Gburek BM. Acquired cystic disease and renal adenocarcinoma following renal transplantation. *J Urol* 1994; 151: 129–132
4. Ito F, Nakazawa H, Ryoji O, Okuda H, Osaka Y, Toma H. Mutagen accumulated in cyst fluid of acquired cystic disease of the kidney. *Nephron* 2000; 86: 192–194
5. Hoshida Y, Nakanishi H, Shin M, Satoh T, Hanai J, Aozasa K. Renal neoplasias in patients receiving dialysis and renal transplantation: clinico-pathological features and P53 gene mutations. *Transplantation* 1999; 68: 385–390
6. Ishizuka T, Hayashi T, Nakazawa H *et al*. Serum vascular endothelial growth factor is a candidate biomarker of renal cell carcinoma in hemodialysis patients. *Nephron* 2000; 84: 83–84
7. Doublet JD, Peraldi MN, Gattegno B, Thibault P, Sraer JD. Renal cell carcinoma of native kidneys: prospective study of 129 renal transplant patients. *J Urol* 1997; 158: 42–44
8. Peces R, Alvarez-Navascués R. Unilateral renal cell carcinoma with coexistent renal disease: a rare cause of end-stage renal disease. *Nephrol Dial Transplant* 2001; 16: 291–294
9. Bostwick DG, Eble JN. Diagnosis and classification of renal cell carcinoma. *Urol Clin North Am* 1999; 26: 627–635
10. Chung-Park M, Parveen T, Lam M. Acquired cystic disease of the kidneys and renal cell carcinoma in chronic renal insufficiency without dialysis treatment. *Nephron* 1989; 53: 157–161
11. Kovacs G. High frequency of papillary renal-cell tumours in end-stage kidneys—is there a molecular genetic explanation? *Nephrol Dial Transplant* 1995; 10: 593–596
12. Hughson MD, Schmidt L, Zbar B *et al*. Renal cell carcinoma of end-stage renal disease: a histopathologic and molecular genetic study. *J Am Soc Nephrol* 1996; 7: 2461–2468
13. Hughson MD, Bigler S, Dickman K, Kovacs G. Renal cell carcinoma of end-stage renal disease: an analysis of chromosome 3, 7, and 17 abnormalities by microsatellite amplification. *Mod Pathol* 1999; 12: 301–309
14. Mourad WA, Nestok BR, Saleh GY, Solez K, Power RF, Jewell LD. Dysplastic tubular epithelium in normal kidney associated with renal cell carcinoma. *Am J Surg Pathol* 1994; 18: 1117–1124
15. Lindblad P, Chow WH, Chan J *et al*. The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 1999; 42: 107–112
16. Chow WH, Gridley G, Fraumeni JF, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000; 343: 1305–1311
17. Liu JS, Ishikawa I, Horiguchi T. Incidence of acquired renal cysts in biopsy specimens. *Nephron* 2000; 84: 142–147
18. Kliem V, Kolditz M, Behrend M *et al*. Risk of renal cell carcinoma after kidney transplantation. *Clin Transplant* 1997; 11: 255–258
19. Takebayashi S, Hidai H, Chiba T, Irisawa M, Matsubara S. Renal cell carcinoma in acquired cystic kidney disease: volume growth rate determined by helical computed tomography. *Am J Kidney Dis* 2000; 36: 759–766
20. Gulanikar AC, Daily PP, Kilambi NK, Hamrick-Turner JE, Butkus DE. Prospective pretransplant ultrasound screening in 206 patients for acquired renal cysts and renal carcinoma. *Transplantation* 1998; 66: 1669–1672


*Received for publication: 9.6.02*
*Accepted in revised form: 7.5.04*