Collecting Duct Carcinoma of The Kidney: Analysis of 74 Cases From Multiple Centers

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Abstract

Objectives

Collecting duct carcinoma (CDC) of the kidney is a rare, aggressive histological subtype of renal cell carcinoma (RCC). We aimed to comprehensively describe the nature of the CDC.

Materials and Methods

We retrospectively collected data from 74 patients with CDC from two centers between January 2001 and December 2020. The clinical characteristics, imaging and pathological features, and diagnostic and treatment methods were analyzed. The Kaplan-Meier method was used to calculate overall survival (OS).

Results

The mean age of the patients was 61.5 years, and 54.1% were males. The most common symptoms were low back pain (39.2%), hematuria (29.7%), and fatigue (14.9%). Computed tomography (CT) was not specific, with 10.8% of the patients diagnosed with urothelial carcinoma and 4.1% with infectious disease. Thirty-two patients had metastasis to the lymph node (32.4%), bone (13.5%) and lung (8.1%) at presentation, while 17.6% had tumor thrombus in the venous system. Twenty-two patients underwent renal biopsy, and 50% of the patients were diagnosed with CDC. Sixty-one renal surgeries were performed, and the pathological median diameter of the CDC was 6.5 cm. Eight patients received immune checkpoint inhibitors (ICIs), and the objective remission rate (ORR) was 50%. The median follow-up time was 16 months, while the median overall survival (OS) was 24.0 months. The Univariate analysis showed that lymph node metastasis, distant metastasis, sarcomatoid differentiation, increasing stage, and absence of renal surgery were predictors of mortality.

Conclusions

CDC is highly aggressive. Patients are commonly diagnosed at an advanced stage. Early surgical treatment can improve prognosis. Though there is still a lack of standard treatment, ICIs bring new hope for the treatment of CDC.

Introduction

Collecting duct carcinoma (CDC), also known as Bellini duct carcinoma, is a rare but highly aggressive type of renal cell carcinoma (RCC). It accounts for 1–2% of all RCC cases [1]. The CDC originates from the distal renal tubular epithelium, which is more similar to urinary epithelial cells than renal cells [2]. CDC usually occurs in young and middle-aged men, with a median age of 55 years. Patients commonly present with clinical symptoms, such as low back pain, hematuria, and systemic symptoms [2].

The clinical diagnosis of CDC is difficult due to its lack of specificity in radiologic examinations. Because of its high aggressiveness, lymph nodes or distant metastases are often already present at diagnosis.

Furthermore, patients may suffer from recurrence and metastasis after surgery, which makes treatment extremely difficult. Currently, there is no standard treatment for this disease. Surgical treatment should be performed as soon as possible for patients with localized CDC, but the significance of cytoreductive nephrectomy remains controversial in patients with metastatic CDC (mCDC). Chemotherapy has some effects on the treatment of mCDC; however, 60–70% of patients die within 1–3 years [3, 4]. However, immune checkpoint inhibitors (ICIs) have been widely used in metastatic clear cell RCC (ccRCC) and urothelial carcinoma (UC). A few case reports have confirmed the effectiveness of ICIs in the treatment of CDC. This brings new hope for the treatment of CDC [5, 6, 7].

Because of its rarity, studies on CDC have mainly been case reports, and the largest study to date involved 577 cases, which were obtained from the National Cancer Database [8]. In this study, we aimed to analyze 74 cases of CDC, which occurred in a period of 20 years in two hospitals. We systematically described the clinical features, methods of diagnosis and treatment, and prognosis of CDC with a large cohort.

Material And Methods

Studies involving human participants were reviewed and approved by the Medical Ethics Committee of Zhejiang Cancer Hospital and Peking University First Hospital. We retrospectively collected 74 cases of CDC, of which 18 patients were diagnosed at the Cancer Hospital of the University of the Chinese Academy of Sciences, while the remaining 58 were diagnosed at the Peking University First Hospital between January 2001 and December 2020. The clinical data of these patients, including demographic data, presentations, imaging features (enhanced computed tomography, CT), pathology, and treatment of CDC, were collected. The number, location, size, and enhancement characteristics of the renal lesions were evaluated by a specialized radiologist. Biopsy or surgical specimens were evaluated by pathologists, and immunohistochemical staining was performed to confirm the diagnosis. Surgical methods included radical nephrectomy, partial nephrectomy, tumor thrombectomy for tumor thrombus, and nephroureterectomy for suspected UC. Other treatment methods included intravenous chemotherapy (gemcitabine + platinum), targeted therapy, radiotherapy, and immunotherapy (ICIs).

The included patients (n = 58) were followed up to record recurrence, metastasis, and survival status. The overall survival (OS) of the patients pertained to the time from the diagnosis of RCC to the last follow-up or death.

Classified variables and continuous variables were tested using the χ^2 test and t-test, respectively. OS was calculated using the Kaplan-Meier method for the study population. The multivariate Cox regression analysis was used to explore factors influencing prognosis. All statistical analyses were performed using the IBM SPSS Statistics for Windows, version 19. Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

The demographic details of the patients with CDC are presented in Table 1. The median age was 61.5 years old (25–83 years old), and 54.1% (40/74) of the patients were male. Around 74.3% of the patients presented with clinical manifestations, such as lower back pain (39.2%), hematuria (29.7%), and fatigue (14.9%).

Table 1
Demographic and clinical characteristics of the patients with
collecting duct carcinoma.

Median age (range)		61.5 (25–83)
No. sex (%)	M	40 (54.1)
	F	34 (45.9)
No. presentation (%)	Incidental	19 (25.7)
	Symptomatic	55 (74.3)
No. symptom (%)	Gross hematuria	22 (29.7)
	Back pain	29 (39.2)
	General fatigue	11 (14.9)
Smoking (%)	Y	15 (20.3)
	N	59 (79.7)
Family history of tumor (%)	Y	9 (12.2)
	N	65 (87.8)
Median BMI (kg/m2) (range)		23.3 (16.0-31.1)

Tumor Characteristics

One patient (1.4%) had bilateral CDC, while 73 had unilateral CDC, including 37 cases on the left side and 36 cases on the right side. Metastasis at presentation was observed in 32 patients (43.2%). In particular, the metastatic sites included the lymph nodes (32.4%), bones (13.5%), lungs (8.1%), liver (5.4%), brain (2.7%), and adrenal gland (5.4%). Tumor thrombus in the renal vein or inferior vena cava was observed in 13 patients (17.6%) (Table 2).

Table 2
Tumor characteristics of the study cohort.

Median diameter of renal mass (cm) (range)		6 (1.4–19)
Clinical diagnosis	RCC	63 (85.1)
	TCC	8 (10.8)
	Infection or inflammation	3 (4.1)
Metastasis status (%)	Y	32 (43.2)
	N	42 (56.8)
Metastatic site (%)	Lymph node	24 (32.4)
	Bone	10 (13.5)
	Brain	2 (2.7)
	Lung	6 (8.1)
	Liver	4 (5.4)
	Adrenal gland	4 (5.4)
	Soft tissue	1 (1.4)
Tumor thrombus	Y	13 (17.6)
	N	61 (82.4)
Renal biopsy	Y	22 (29.7)
	N	52 (70.3)
No. primary treatment	Surgery	61 (82.4)
	Chemotherapy	8 (10.8)
	Chemotherapy + Immunotherapy	1 (1.4)
	Target therapy	3 (4.1)
	Target therapy + Immunotherapy	1 (1.4)
Type of surgery	Radical nephrectomy	49 (66.2)
	Partial nephrectomy	2 (2.7)
	Nephroureterectomy	9 (12.2)
	Biopsy	1 (1.4)

In terms of enhanced CT, tissues with CDC exhibited low to moderate enhancement (89.3%), uneven texture (73.3%), blurred boundary (60%), endogenous growth (56.7%), cystic components (16.7%), necrosis (8.3%), and bleeding (1.7%) (Table 3). Radiologically, 10.8% of the patients were diagnosed with UC, while 4.1% had infectious diseases. Twenty-two patients (29.7%) underwent renal puncture biopsy. Of these, 50% were diagnosed with CDC, 45.5% with untyped RCC, and 4.6% with UC.

Table 3
Radiological features (enhanced computed tomography, CT) of the study cohort.

Radiological evaluation		Number (%)
Enhancement	Y	56 (93.3)
	N	4 (6.7)
Enhancement pattern	Low/ mildly high	50 (89.3)
	High	6 (10.7)
Internal texture of renal mass	Homogeneous	16 (26.7)
	Heterogeneous	44 (73.3)
Well-defined margin	Y	24 (40)
	N	36 (60)
Growth pattern	Exophytic	26 (43.3)
	endophytic	34 (56.7)
Component	Solid	50 (83.3)
	cystic	10 (16.7)
Renal vein or inferior vena cava thrombosis	Y	13 (17.6)
	N	61 (82.4)
Hemorrhage	Y	1 (1.7)
	N	59 (98.3)
Necrosis	Y	5 (8.3)
	N	55 (91.7)

Treatment

Surgery was performed in 61 patients (82.4%) as primary treatment. Radical nephrectomy, partial nephrectomy, total nephroureterectomy, and open biopsy of the renal tumor were performed in 66.2%,

2.7%, 12.2%, and 1.4% of cases, respectively (Table 2). Among the 18 CDC patients with distant metastases, eight underwent cytoreductive surgery.

For the patients who did not undergo renal surgery, eight patients received chemotherapy with a gemcitabine + platinum (GC) regimen. Three patients demonstrated partial response (PR); two patients maintained stable disease (SD). One who received chemotherapy combined with ICI had SD. There was no obvious response to targeted therapy in the three patients. One patient received targeted therapy combined with immunotherapy as neoadjuvant therapy and achieved PR, which was followed by nephrectomy (Table 2).

Pathology

The pathological features of the patients with CDC are presented in Table 4. The median tumor diameter was 6.5 cm (0.4–22 cm) pathologically. In terms of nuclear grade, 5.4% had grade 2; 64.9% had grade 3; and 23.0% had grade 4. Necrosis, sarcomatoid, squamous, and neuroendocrine differentiation were observed in 47.3%, 25.7%, 5.4%, and 1.4% of the patients, respectively (Table 4). Interestingly, one patient had UC in the same kidney. The pathological stage was pT1 in 12 cases (16.2%), pT2 in 8 (10.8%), pT3a in 29 (39.2), pT3b in 7 (9.5), pT4 in 5 (6.8), and not available in 13 (17.6%). Immunohistochemical high-expression molecules included AE1/AE3, CK7, CK8/18, vimentin, EMA, CD10, and Pax-8, with positive rates of 100%, 62.7%, 94.7%, 73.8%, 85.7%, 58.2%, and 60%, respectively. The average Ki67 positivity rate was 40%.

Table 4

Pathological features of the patients with collecting duct carcinoma.

Median tumor diameter (cm) (range		6.5 (0.4–22)
No. Fuhrman grade (%)	1	0 (0)
	2	4 (5.4)
	3	48 (64.9)
	4	17 (23.0)
	Not available	5 (6.8)
Necrosis (%)	Y	35 (47.3)
	N	39 (52.7)
Sarcomatoid (%)	Y	19 (25.7)
	N	55 (74.3)
Squamous differentiation (%)	Y	4 (5.4)
	N	70 (94.6)
Neuroendocrine differentiation (%)	Y	1 (1.4)
	N	73 (98.6)
Clear cell carcinoma component (%)	Y	5 (6.8)
	N	69 (93.2)
Pathological Stage (%)	T1	12 (16.2)
	T2	8 (10.8)
	T3a	29 (39.2)
	T3b	7 (9.5)
	T3c	0 (0)
	T4	5 (6.8)
	Not available	13 (17.6)

Prognosis

A total of 58 patients were followed up for a median of 16 months (2-137 months). At the last follow-up, 36 patients died, while 22 survived. They had a median OS of 24.0 months (Fig. 1).

Among the patients with postoperative metastasis, one patient received radiotherapy, and the response was PR. Five patients were treated with ICIs; one had CR, one had PR. The patient with CR survived for 58 months. One patient received targeted therapy combined with immunotherapy and achieved a PR. Five patients received targeted therapy, and one patient achieved SD. Four patients underwent chemotherapy, and one patient responded to PR.

Univariate analysis showed that the absence of lymph node metastasis, distant metastasis, and sarcomatoid degeneration; earlier stage; and surgical treatment could be used to predict a better survival (Table 5). For patients with mCDC, cytoreductive surgery had no significant effect on survival time (7 vs. 9 month, $P = 0.819$) .

Table 5
Univariate survival analysis and multivariable analysis of
patients with collecting duct carcinoma.

Variable		Overall survival		
Single factor analysis		p		
Gender		0.971		
Age (yr)	=<60	0.303		
	> 60			
Smoking history		0.815		
Family history of tumor		0.185		
Symptoms		0.348		
Tumor thrombus		0.705		
Lymph node metastasis		0.001		
Distant metastasis		0.004		
Surgery		< 0.001		
Size	=<7cm	0.593		
	> 7cm			
Stage	I/II	0.045		
	III/IV			
Necrosis		0.470		
Sarcomatoid		0.001		
Multifactor analysis		HR	95% CI	p
Lymph node metastasis		2.156	0.938,4.958	0.070
Distant metastasis		1.453	0.515,4.101	0.480
Surgery		0.489	0.148,1.611	0.239

Discussion

The prognosis of ccRCC has significantly improved with the development of targeted therapy and immunotherapy [9]. However, CDC, as a rare type of renal non-ccRCC, still poses great challenges to oncologists because of its aggressiveness and poor therapeutic response. Here, we analyzed 74 patients with CDC from two high-volume centers in a span of 20 years. By comprehensively describing the clinical

features, imaging findings, diagnosis and treatment courses, and pathological features of patients with CDC, we hereby provide a reference with a large sample study.

CDC is likely to present with clinical symptoms. In fact, about 65.2% of the patients had symptoms according to previous studies [10, 11]. The percentage of patients with symptoms in our study was 74.3%, which was significantly higher than that of patients with ccRCC [12]. This might be associated with the high aggressiveness and rapid progression of CDC. Patients with CDC likely presented with hematuria. Tokuda et al. reported that the incidence of hematuria in patients with CDC was 37.0% [11]. In our study, 29.7% of the patients had hematuria. The high incidence of hematuria may be related to the nature of CDC, which can easily invade the collecting system.

The incidence of venous tumor thrombus in RCC is 4% [13]. The occurrence of venous tumor thrombus is associated with the tumor size, stage, and grade. In addition, tumor thrombus is a predictor of poor outcomes [13]. However, the incidence of tumor thrombus in patients with CDC has not been previously reported. Here, we reported that 17.6% of CDC patients had a tumor thrombus. The higher incidence of tumor thrombus in CDC may be related to CDC's aggressiveness, high nuclear grade, and advanced stage. In addition, the presence of a tumor thrombus greatly increases the difficulty of CDC surgery.

The clinical diagnosis of CDC mainly depends on imaging examinations, and CT is the most common method. On CT scan, CDC tumors are solitary, solid, and poorly defined. They have cystic components, calcifications, and lymph node metastases. In addition, they are centered in the medulla, which results in the compression of the renal pelvis [14]. The degree of enhancement of the lesion was lower than that in the normal renal cortex and medulla. This suggests that the tumor is atypical with a lack of blood supply [15]. The differential diagnoses for CDC included invasive transitional cell or squamous cell carcinoma of the renal collecting system, renal lymphoma, renal metastases, mesoblastic nephroma, renal medullary carcinoma, and bacterial pyelonephritis [15]. Around 61.1% of CDCs were reported to oppress or infiltrate the collecting systems, which was quite difficult to distinguish from UC involving the renal parenchyma [16]. In our study, as many as 10.8% of CDCs were misdiagnosed as UC radiologically. In addition, CDC might not necessarily show a renal mass on imaging. When the tumor infiltrated the entire renal parenchyma, it needed to be distinguished from benign diseases such as renal tuberculosis, pyelonephritis, or xanthogranuloma. Our study showed that three patients with CDC were misdiagnosed with tuberculosis on CT scan. Mathisekaran et al. presented a CDC patient with complaints of low-grade fever, loss of appetite, left loin pain, and dyspnea, which was masquerading as genitourinary tuberculosis. Finally, the patient was diagnosed with CDC after radical nephrectomy [17]. Because some patients with CDC also had symptoms such as fever and weight loss, the possibility of CDC should be considered in patients who were suspected of having renal tuberculosis, but in whom tuberculosis-related tests were negative or anti-tuberculosis treatment was ineffective.

Surgery is the main treatment for localized CDC. Tokuda et al. reported that 98.8% of the 81 CDC patients received surgical treatment, including radical nephrectomy (88.9%), partial nephrectomy (2.5%), and full-length nephroureterectomy (7.4%) [11]. In our study, 82.4% of patients underwent renal surgical

procedures, including radical nephrectomy (66.2%), partial nephrectomy (2.7%), and full-length nephroureterectomy (12.2%). Despite its aggressiveness and poor therapeutic response, some patients with an earlier disease stage may have a better prognosis. Chao et al. reported that one patient with pT1N0M0 cancer remained disease-free at five years of follow-up after nephrectomy [18]. Peyromaure et al. reported that two patients without metastatic disease remained alive at 13 and 17 months after nephrectomy [19]. In our study, 10 patients achieved long-term disease-free survival, and the longest survival time was 147 months after surgery. However, most patients with CDC have lymph nodes and/or distant metastasis at presentation; therefore, radical surgeries in most patients are actually cytoreductive nephrectomy (CNx). Whether CNx is beneficial for metastatic CDCs is currently controversial. In a SEER database study involving 62 mCDC patients, the cancer-specific survival of patients who received CNx was significantly better than that of patients who did not [20]. Another report from the National Cancer Database showed that the OS of CNx + chemotherapy was significantly longer than that of surgery or chemotherapy alone. However, there was no significant difference in survival between patients with CNx and those who received chemotherapy alone [8]. In addition, considering the advanced stage and venous tumor thrombus of the CDC, the perioperative risk of CNx is quite high. Méjean et al. reported 10 cases of CDC patients undergoing renal surgery, of which three patients died after surgery, and the median OS after surgery was 6 ± 8 months. Therefore, the authors did not recommend surgery alone for patients with mCDC [21]. Our study revealed that for metastatic CDC, whether to undergo CNx had no significant effect on survival time. However, due to the small sample size and selection bias in this study, future studies with larger sample sizes are needed to confirm the significance of CNx in patients with mCDC.

The biological behavior of CDC is similar to that of UC; therefore, the NCCN guidelines recommend chemotherapy as a treatment option for patients with mCDC [22]. In a multicenter prospective study, 23 patients with mCDC with no prior systemic chemotherapy were treated with gemcitabine plus cisplatin or carboplatin. They demonstrated an ORR of 26%, a median OS of 10.5 months, and a median progression free survival (PFS) of 7.1 months [3]. In another prospective, phase 2 trial, 26 mCDC patients with no prior systemic chemotherapy were treated with sorafenib combined with chemotherapy (gemcitabine plus cisplatin). The results showed that PFS and OS were 8.8 months and 12.5 months, respectively, with the ORR being 30.8% [4]. Moreover, Pécuchet et al. reported five previously untreated patients with mCDC who received bevacizumab in combination with gemcitabine and platinum salt with three cases of PR, one case of SD, and one case of complete remission after surgery of the only metastatic site [23]. In our study, 12 patients received chemotherapy (gemcitabine combined with cisplatin), with three patients achieving PR. This finding suggests that chemotherapy is a relatively effective treatment for mCDCs.

ICIs have become one of the main treatments for advanced RCC. However, their application in patients with CDC is mainly based on case reports [6, 7, 24, 25]. Mizutani et al. reported a case of mCDC treated with nivolumab after chemotherapy and targeted therapy, and the lung metastasis was completely relieved, while the lymph node metastasis remained stable [7]. Watanabe et al. reported that an mCDC patient was treated with nivolumab and ipilimumab after cytoreductive nephrectomy. This resulted in complete relief from lymph node metastasis [24]. In our study, 8 patients with mCDC were treated with ICIs alone or ICIs combined with chemotherapy/targeted therapy as first or second line of therapy. These

treatment regimens resulted in good responses and the ORR achieved as high as 50%. Therefore, ICIs can be another treatment option for patients with mCDC.

For CDC patients, previous studies have shown that an American Society of Anesthesiologists (ASA) score of 3–4, tumor size greater than 7 cm, M1 stage, a Fuhrman grade of 3–4, and the presence of lymphovascular invasion independently predicted disease-specific mortality [26]. Wilson et al. reported that T stage $\geq$ T3, high nuclear grade, distant metastasis, surgical treatment, and surgery combined with chemotherapy/radiotherapy are prognostic factors for CDC [8]. Taguchi et al. described another independent negative prognostic marker, neutrophil/lymphocyte ratio, and stated that a ratio $\geq$ 4 was associated with poor CSS [27]. Our study showed that no lymph node metastasis, distant metastasis, earlier stage, sarcomatoid differentiation, and surgery predicted longer OS in patients.

The present study has several limitations. First, our series has all the limitations inherent to retrospective evaluations, such as susceptibility to recall bias and selection bias. Second, due to the long duration of the study, there was incomplete clinical data for several patients, and there was a high rate of patients lost to follow-up. Third, the decision-making of the treatment plan was often based on the patient's condition and general conditions, which might have caused selection bias in the treatment decision, resulting in differences in the condition of the group in the univariate analysis, thereby affecting the accuracy of the results.

Conclusions

In conclusion, CDC is a rare subtype of RCC, which is highly aggressive and is associated with a high rate of metastasis and poor prognosis. In addition, it has no standard treatment. Low back pain and hematuria are the common symptoms. Imaging examinations and biopsy pathology can assist in the diagnosis, but the accuracy is not high. Radical surgery is the only curative treatment for patients with localized CDC. However, it is prone to recurrence and metastasis after surgery. Metastatic patients receiving targeted therapy lack efficacy. Furthermore, chemotherapy and immunotherapy have better benefits.

Declarations

Acknowledgement

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Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Ethics Committee of Zhejiang Cancer Hospital and Peking University First Hospital with approval number IRB-2021-69 and in accordance with the Declaration of Helsinki. The patients provided written consent.

Conflict of Interest

No potential conflicts of interest to disclose.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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None.

Author Contributions

Jinchao Chen and Desheng Cai were contributed equally. Shaoxing Zhu was responsible for the concept and design of the study. Jinchao Chen, Desheng Cai, Kan Gong, Hua Wang, Zongping Wang dealt with the clinical data. Jinchao Chen performed the statistical work and drafted the manuscript. Desheng Cai provided the figures and tables. All authors revised the manuscript.

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Figures

Figure 1

Kaplan Meier curves of overall survival of the patients with collecting duct carcinoma.