Collecting Duct Carcinoma

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7.1 Introduction

Collecting duct carcinoma (CDC) of the kidney is a rare variant of renal cell carcinoma (RCC) with an extremely poor prognosis as most cases are metastatic at the time of diagnosis. RCC is a clinically, histologically and genetically heterogeneous group of tumours. The different subtypes of RCC are classified according to the cells of origin in the different parts of the nephron. Conventional (clear cell) RCC and papillary RCC show alterations linked to the proximal tubules, while chromophobe RCC and CDC are presumed to originate from the collecting duct epithelium (intercalated cells and principal cells of the collecting ducts, respectively). The collecting ducts in the kidney are also known as the Bellini's ducts, named after the Italian physician Lorenzo Bellini (1643–1704) who described these tubes for the first time (ref: https://www.britannica.com/biography/Lorenzo-Bellini). This explains why CDC is also known as Bellini duct carcinoma. Of all renal neoplasms, CDC is the most aggressive with no established treatment guidelines [1, 2].

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7.2 Recognition as a Unique Pathological Subtype of RCC

In 1976, Mancilla-Jimenez and colleagues first observed the atypical hyperplastic changes of adjacent collecting duct epithelium in 3 out of 34 cases of papillary RCC. The authors suggested that some papillary RCC may arise from the epithelium of the collecting ducts [3]. Since 1986, CDC is recognized as a new separate entity [4, 5]. In 1997, the Heidelberg classification of renal tumours identified five histologic types of RCC: conventional (clear cell), papillary, chromophobe, collecting duct and unclassifiable [1, 6]. In the 2004 World Health Organization (WHO) classification, CDC was also recognized as a distinct entity from conventional, papillary and chromophobe RCC [7]. Recently, new subtypes of RCC have been described: hereditary leiomyomatosis and RCC, syndrome-associated RCC, succinate dehydrogenase-deficient RCC, tubulocystic RCC, acquired cystic disease-associated RCC and clear cell papillary RCC [8, 9]. Each type has distinct histological (light and electron microscopy), immunohistochemical and cytogenetic features [9].

7.3 Epidemiology

CDC is a rare tumour of the kidney that accounts for 1–3% of all renal neoplasms [10–16]. It occurs at almost any age (range, 13–83 years) with a mean age of 55 years and predominantly affecting males (male to female ratio is 2:1) [17]. A retrospective study using the Surveillance, Epidemiology, and End Results (SEER) cases from 1973 to 2004 identified 98 patients with CDC. According to this study, 63.3% of these patients are white, 27.5% are African American and 9.2% are other races [18]. A total of 160 CDC patients were present in the SEER database from 2001 to 2005. Compared to patients with clear RCC, CDC occurs more frequently in African Americans (23% vs. 9%) [10].

7.4 Clinical Symptoms

Similar to RCC, patients with CDC usually present with abdominal pain, palpable flank mass and gross haematuria. Systemic features as anorexia, weight loss, fatigue and fever are also occasionally present [17]. Approximately one third of patients have metastases at presentation [7]. The most common metastatic sites are the regional lymph nodes, lungs, bone and liver [14].

7.5 Imaging Examinations

Early detection is probably the only factor leading to a prolonged survival for patients with CDC. However, it remains challenging to reliably suggest the diagnosis of CDC based on imaging findings. To date, the imaging features of CDC are not well described, since only case reports or studies involving small numbers of patients have been published [19].

Pickhardt et al. (2001) analysed the radiological observations of 17 patients with histopathologically confirmed CDC. Medullary involvement in small tumours and infiltrative appearance in larger tumours were common findings and may suggest the diagnosis of CDC. In larger tumours, however, these features are frequently associated with an exophytic or expansile component that cannot be distinguished from conventional RCC [20]. Yoon et al. (2006) retrospectively reviewed the CT scans of 18 patients with pathologically proven CDC. The authors reported that medullary location (94%), mild (69%) and heterogeneous (85%) enhancement, involvement of the renal sinus (94%), infiltrative growth (67%), preserved renal contour (61%) and a cystic component (50%) were CT findings frequently observed in CDC patients [21]. More recently, Hu et al. (2014) analysed the imaging features of six CDC patients. The results of the study indicated medullary location, moderate and heterogeneous enhancement, infiltrative growth, damage of renal function in the involved kidney and a marked uptake of ^{18}F-FDG on PET/CT imaging were imaging observations commonly identified. The hypovascular parts of bulky tumours are more likely to be explained by a desmoplastic stromal reaction rather than by tumour necrosis. Nevertheless, these CT findings are non-specific and may not allow CDC to be easily differentiated from other subtypes of RCC. However, when a renal tumour shows these imaging features, CDC may be suggested as a possible differential diagnosis [22]. Figure 7.1 presents contrast enhanced CT images, axial scan and coronal reformatted image, showing a CDC in the upper pole of the left kidney, with lymph node metastasis and pulmonary metastasis.

Also magnetic resonance imaging (MRI) findings are non-specific for CDC. Zhu et al. (2013) retrospectively studied 20 patients with CDC using multisection computed tomography (MSCT) ($n = 20$) or MSCT and MRI ($n = 5$). MRI revealed cystic components, poorly defined tumour borders, isointense tumour on T1-weighted imaging and iso- or hypointense tumour on T2-weighted imaging. Enhancement was reduced within the tumour compared to the renal cortex and medulla [23]. Table 7.1 summarizes the CT and MRI findings frequently observed in CDC patients.

As CDC does not have specific imaging features that distinguish it from other types of RCC, histopathological and immunohistochemical examinations are required for a final diagnosis of CDC.

7.6 Macroscopic Findings

CDCs are usually centrally located within the kidney. When the tumour is small, origin within the renal medulla may be seen. When it is large, irregular extensions into the adjacent renal cortex may be present. Some tumours may extend into the renal pelvis. Local invasion into perirenal and sinus fat can be found. Reported tumour size ranges from 2.5 to 12 cm in diameter (mean 5 cm diameter). They have a grey-white appearance with irregular borders and a firm consistency on sectioning. Tumour necrosis and satellite nodules may be present. Haemorrhage is not usually seen macroscopically [17, 24].

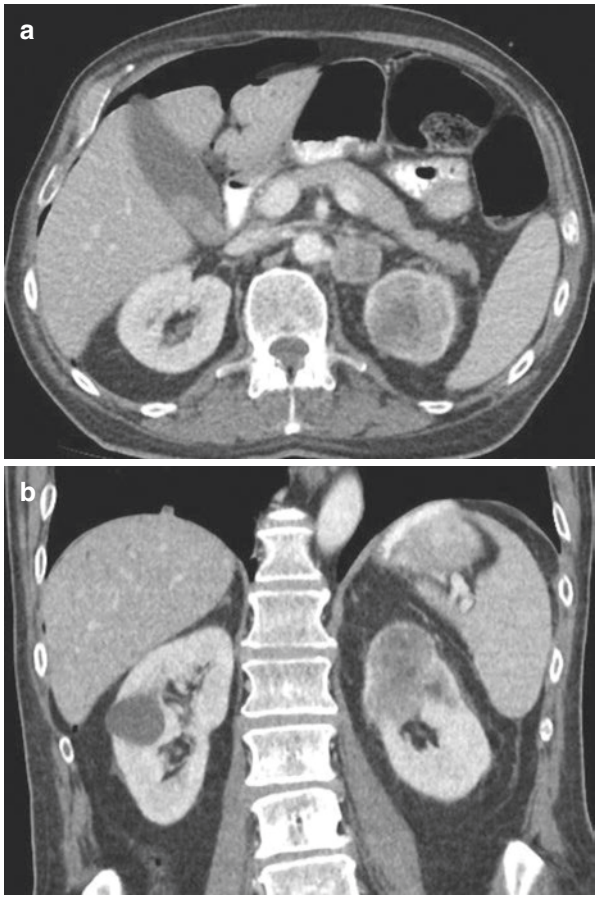

Fig. 7.1 Collecting (Bellini) duct carcinoma: Contrast-enhanced CT images, axial scan (**a**) and coronal reformatted image (**b**) showing a hypovascular infiltrating tumour in the upper pole of the left kidney, with preservation of the renal shape. Metastatic para-aortic lymph nodes (**a**). A lung metastasis is visible at the right diaphragmatic dome (**b**)

Table 7.1 CT and MRI findings frequently observed in CDC patients

CT	Medullary location Mild and heterogenous enhancement Involvement of the renal sinus Infiltrative growth Preserved renal contour Cystic component
MSCT or MSCT and MRI	Cystic components Poorly defined tumour borders Isointense tumour on T1-weighted imaging Iso- or hypointense tumour on T2-weighted imaging Enhancement reduced within tumour compared to the renal cortex and medulla

CT computed tomography, *MRI* magnetic resonance imaging, *MSCT* multisection computed tomography

7.7 Histopathology

CDC originates from the collecting duct epithelium that arises from the mesonephros (Wolffian duct) as do the ureter, renal pelvis and calyces. It is an ill-defined tumour, consisting of anastomosing tubules, cords and nests of tumour cells, frequently with a variety of growth patterns within the same tumour. When extending into the renal cortex, CDC typically infiltrates between the glomeruli, a feature also seen in urothelial cell carcinoma (UCC) but rarely in RCC. Malignant cells have variable amounts of cytoplasm and often pleomorphic nuclei. A 'hobnail' pattern can be present, when the nuclei are apically located within the cells protruding towards the lumen of the tubules. If present, this is a useful characteristic as it is rarely found in other types of RCC (except for type 2 papillary RCC) and not in UCC. Mitotic figures are frequently present. Sarcomatoid dedifferentiation has been reported. Intraluminal mucin production (absent in RCC) staining, positive on periodic acid-Schiff (PAS) and mucicarmine stains, can be seen [17]. Atypical cells can be found in adjacent non-invasive distal tubules or collecting ducts, giving a clue to the collecting duct origin of the tumour. The epithelial structures are lying in an abundant, loose or desmoplastic stroma.

In some reported cases, a papillary architecture predominates, giving rise to a differential diagnostic problem with papillary RCC [17]. The clinical and pathobiological aspects of CDC and papillary RCC were described in more detail by Kuroda et al. (2002, 2003) [24, 25]. Other differential diagnoses are UCC with glandular differentiation, adenocarcinoma arising from the pelvic urothelium and metastatic carcinoma. As the microscopic appearance of CDC is inconsistent, diagnosis on histological criteria alone is not pathognomonic, and immunohistochemical staining is necessary to show the origin of the tumour [7, 17, 24] (Fig. 7.2).

7.8 Immunohistochemical Findings

CDCs express pankeratin, high molecular weight keratins (HMWK) [34βE12, keratin 19 (K19)] and *Ulex europaeus* lectin, as do non-malignant collecting ducts. Tumours usually also show positivity for E-cadherin. Keratin 7 (K7) and epithelial membrane antigen (EMA) reactivity is variable. CD15 (LeuM1), a marker of the proximal tubular epithelium, is negative [7, 14, 17, 26–30]. Other markers of proximal renal tubules (CD10, RCC antigen and α-methylacyl-CoA racemase (AMACR)) are almost always negative [29].

The differential diagnosis of CDC from UCC and papillary RCC is often challenging. The hypothesized association between CDC and UCC, based on similar embryologic origin (mesonephros), has been confirmed in immunohistochemical studies in which both tumour types expressed *Ulex europaeus* lectin and HMWK (both negative in RCC). The three kidney tumours of which two were classified as CDC and one as UCC were negative for cytokeratin 20 (K20) and vimentin [28].

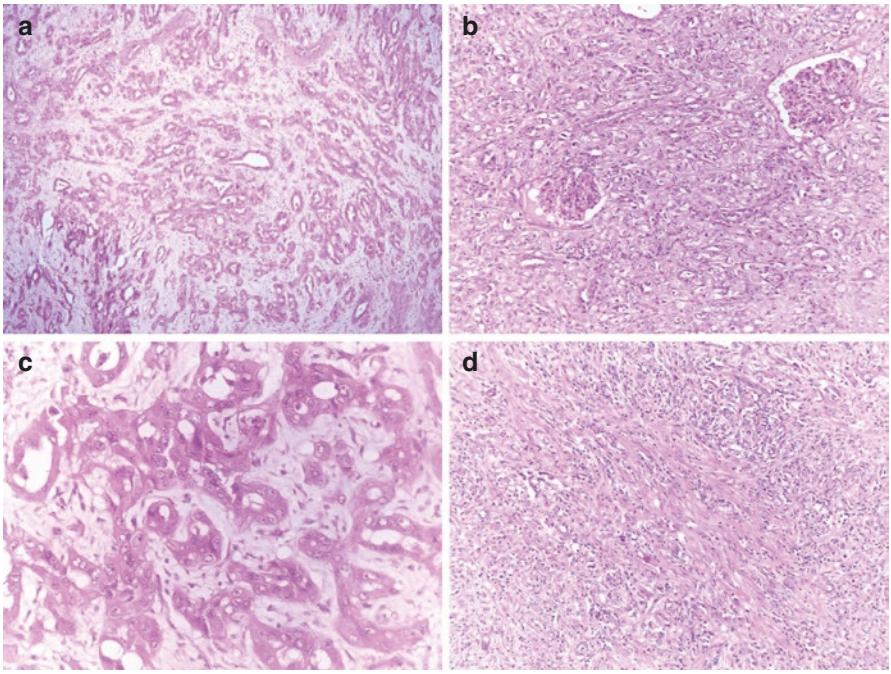

Fig. 7.2 The most typical growth pattern of CDC is a tumour consisting of tubuloglandular structures (panel **a**). However, often the tumour loses this pattern and grows very infiltrative as nests, strands and single cells. This explains the ill-defined borders of CDC. When expanding into the cortex, tumoural cells intersperse between glomeruli (panel **b**). Note the marked nuclear pleomorphism (panel **c**) and the desmoplastic stroma reaction (panel **d**)

Kobayashi et al. (2008) examined the use of adopting immunohistochemical markers for the differential diagnosis of 17 cases of CDC, 10 cases of invasive UCC and 15 cases of papillary RCC. The authors reported that *Ulex europaeus* agglutinin 1 reactivity and positivity for E-cadherin and c-KIT are useful in differentiating CDC from papillary RCC as well as negative results for AMACR and CD10 are potentially useful hallmarks of this distinction. In contrast, using immunohistochemistry with these antigens is not of value in distinguishing CDC and invasive UCC. Therefore, the authors concluded that the differential diagnosis for CDC and invasive UCC requires careful evaluation of clinical information, and macroscopic and microscopic findings, including the intraepithelial lesion of the pelvic urothelial mucosa [31]. Later, Albadine et al. (2010) evaluated the use of the combination of PAX8 and p63 in the differential diagnosis of 21 cases of CDC and 34 cases of upper urinary tract urothelial cell carcinoma (UUT-UCC). The authors showed that the immunoprofile of PAX8+/p63- strongly favoured a diagnosis of CDC, whereas a profile of PAX8−/p63+ favoured UUT-UCC [32]. Gonzalez-Roibon et al. (2013) investigated whether adding the GATA binding protein 3 (GATA3) to this combination might improve its performance in the differential diagnosis of 18 CDC cases and 25 UUT-UCC cases. They found that GATA3 positivity was higher in

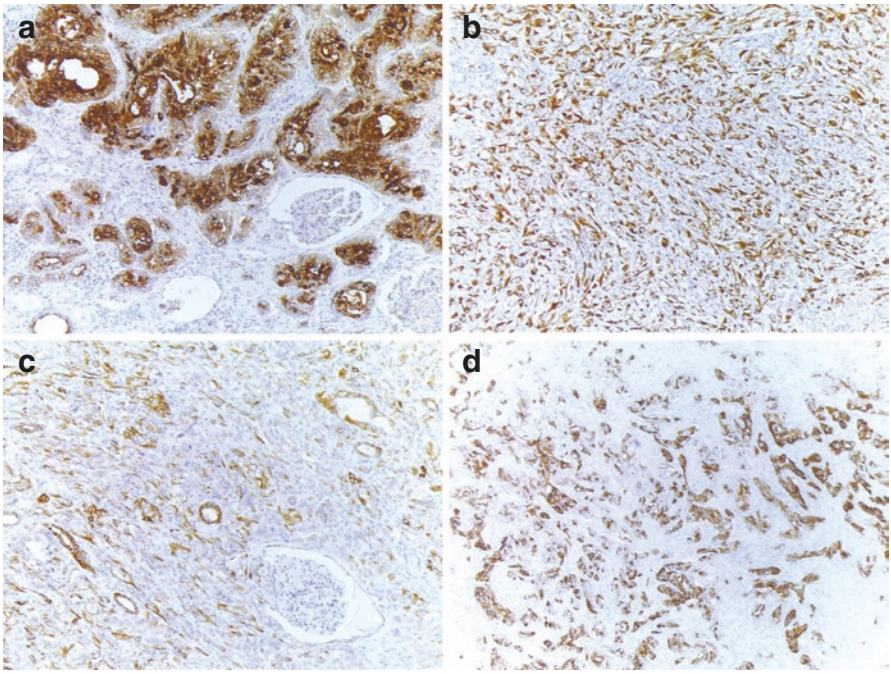

Fig. 7.3 CDC shows cytoplasmic positivity for *Ulex europaeus* lectin (variable staining intensity) (panel **a**). K19 positivity of CDC. In the given case, the picture was taken in an area of pseudosarcomatous dedifferentiation (panel **b**). K7 expression is variable in presence and in staining intensity within CDC (panel **c**). Epithelial membrane antigen (EMA) expression in CDC has been reported as variable. In our hands, it is always positive in CDC (panel **d**)

UUT-UCC (88%) compared to CDC (11%) and that a profile of GATA3 or p63+ and PAX8- strongly favoured a diagnosis of UUT-UCC [33] (Fig. 7.3).

7.9 Diagnostic Criteria

According to the 2016 WHO classification, the diagnostic criteria for CDC are (1) medullary involvement by the tumour, (2) a predominant tubular tumour architecture, (3) epithelial tumoural cells lying within a desmoplastic stroma, (4) high-grade cytology, (5) infiltrative growth pattern and (6) the absence of other renal cell carcinoma subtypes or UCC [9].

7.10 Cytogenetics and Molecular Features

Ancillary cytogenetic techniques, such as conventional karyotyping and fluorescence in situ hybridization (FISH), are not typically helpful for confirmation of diagnosis of CDC. Initial cytogenetic reports are rather confusing, as some have demonstrated

mainly a combination of multiple chromosome losses (chromosomes 1, 4, 6, 14, 15, 18 and 20) [34–38], while others described also trisomies and structural chromosomal abnormalities [39, 40]. Cytogenetic biomarkers have not significantly improved the stratification of patients beyond traditional clinical pathologic variables.

More currently, comparative genomic hybridization (CGH) was used to investigate the genetic composition of patient's tumours. In a multicentre German study, Becker et al. (2013) determined genomic copy number alterations of CDC (29 samples) in comparison to those of UUT-UCC (26 samples). The authors showed that CDC was characterized by a different genomic profile compared to UUT-UCC. Recurrent losses of chromosome regions were detected on chromosomes 8p (n = 9/29), 16p (n = 9/29), 1p (n = 7/29) and 9p (n = 7/29), and recurrent gains were observed at 13q (n = 9/29). Genetic losses on chromosomes 1p36, 3p, 6p and 8p, as well as a gain on chromosome 13, were associated with aggressive disease stages. In contrast to CDC, the most frequently detected UUT-UCC DNA aberration was 9q loss (n = 13/26). DNA losses at 13q and 8q as well as gains at 8p showed significant variations in UUT-UCC compared to CDC [41]. The cytogenetic profile of UUT-UCC has been reported to be identical to that of bladder UCC [42, 43]. In addition, CDC is characterized by a different genetic profile compared to three classic RCC histologies, i.e. conventional, papillary and chromophobe RCC [44, 45]. Cytogenetic alterations of RCC and its different subgroups are well documented and generally accepted in many studies published in the last years [46–49]. The study by Becker et al. (2013) suggests CDC as a unique entity among kidney cancers. However, multi-institutional studies of CDC using a larger number of patients are needed to confirm these preliminary findings [41].

Next-generation massively parallel sequencing studies of CDC aimed at understanding the critical molecular alterations associated with this tumour type have been limited due to the tumour rarity. In a recent report, targeted interrogation of genes known to be implicated in cancer was performed in 17 locally advanced or metastatic CDC tumours. Thirty-six genomic alterations were detected, the most common being *NF2*/22q12 (29%), *SETD2*/3p21.1 (24%), *SMARCB1*/22q11 (18%) and *CDKN2A*/9p21 (12%). In addition, mutations of *PIK3CA*, *PIK3R2*, *FBXW7*, *BAP1*, *DNMT3A*, *VHL* and *HRAS* were also identified in single cases. Notably, these mutations were defined as clinically relevant given their ability to aid in selection of approved targeted therapies [50]. Recent whole exome sequencing and RNA-seq analysis of 7 CDC tumours, as well as additional FISH analysis of *CDKN2A* on 16 tumours, confirmed the frequent loss of *CDKN2A* (62.5% of cases) [51]. Understanding the molecular pathogenesis of CDC will play a key role in the future subclassification of this unique tumour.

7.11 Treatment

Multi-institutional collaboration is required to assemble a sufficiently large number of cases to make statements on possible treatments. Three studies [14–16] relevant to the management of CDC were identified in a systematic review by Dason et al. [52].

7.11.1 Surgery

Evidence for the role of surgery is lacking in the literature. Almost all reported patients with CDC underwent surgery [10, 12, 14, 15, 53] and were diagnosed with CDC after histopathology examination [10, 14, 15, 53]. Eighty-seven percent of the patients in the study of Oudard et al. underwent prior cytoreductive nephrectomy [15]. Mejean et al. (2003) reported three perioperative deaths in their series of ten patients undergoing surgery for CDC. They concluded that because the prognosis is poor despite radical nephrectomy, biopsy should be performed first when radiological findings are suggestive of CDC. For metastatic CDC (mCDC), radical nephrectomy alone does not seem to be useful except for palliative reasons or in combination with new chemotherapy regimen [54]. Abern et al. (2012) examined 227 CDC cases and reported that CDC patients selected for cytoreductive nephrectomy had improved survival [11]. As most CDC patients are already metastatic at presentation, the rate of perioperative morbidity is high and may delay or prevent the patients from receiving systemic treatment [15]. Accordingly, surgical therapy for CDC must be individualized.

7.11.2 Chemotherapy

Based on the clinical similarities between CDC and UCC, Milowsky et al. (2002) suggested that the chemotherapy regimen used for treatment of UCC might also be appropriate for CDC [55]. A prospective multicentre phase II study with central histopathology review evaluated the effect of gemcitabine and either cisplatin or carboplatin (GC) on 23 patients with mCDC. The objective response rate was 26% (95% CI 8–44). Median progression-free survival (PFS) and overall survival (OS) were 7.1 (95% CI 3–11.3) and 10.5 months (95% CI 3.8–17.1), respectively. Of the 23 patients, 87% underwent cytoreductive nephrectomy, and 96% had Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 [15]. It is unknown how the study results would have been in patients who did not undergo surgery. The treatment was associated with manageable adverse events. Toxicity was mainly haematological with grade 3–4 neutropenia and thrombocytopenia in 52% and 43% of patients, respectively. Given the lack of any other beneficial agent, this platinum-based chemotherapy regimen should be considered the standard of care for first-line systemic treatment of mCDC patients [15].

In 2012, a case report presented complete remission of pulmonary metastases and long-term survival in a mCDC patient treated with gemcitabine, cisplatin and bevacizumab [56]. In a more recent study, five patients diagnosed with mCDC received bevacizumab in addition of the GC combination. All patients had undergone radical nephrectomy, but none had received previous systemic treatment for CDC. This new triple treatment regimen resulted in a longer PFS (15.1 months, 95% CI 5.6–20.4) and longer OS (27.8 months, 95% CI 12.4–unreached) (more than double) than recorded in 2007 by Oudard et al. in patients treated with a GC regimen. The French Collaborative Group is currently recruiting patients in a prospective multicentre phase II study (NCT02363751) of this triple treatment regimen

in mCDC [57]. Case reports have also reported responses to paclitaxel [58] and paclitaxel and carboplatin [59].

7.11.3 Immunotherapy

The largest series of CDC treated with immunotherapy is a retrospective series based on a multi-institutional survey (66 Japanese centres) that comprised 81 patients and was confirmed by a central review. In a subpopulation of this study, immunotherapy was used in 34 CDC patients (interferon (IFN-α, INF-γ) or interleukin 2 (IL-2)). No responses were observed [14]. Also in another retrospective study including 15 CDC patients treated with immunotherapy, no therapy effect was recorded [16]. The programmed death-1 and programmed death-ligand 1 (PD-1/PD-L1) targeting antibodies, alone or in combination with anti-angiogenic drugs or other immunotherapeutic approaches, show promising results for the treatment of RCC. A recent study suggested that PD-L1 could represent an important therapeutic target for CDC. However, only 5 of the 101 non-clear cell RCCs in this study were CDC. One of five CDCs were considered PD-L1+, and PD-L1 positivity by tumour-infiltrating mononuclear cells was observed in all 5 CDCs [60]. The efficacy and safety of anti-PD-1/PD-L1 agents in specific RCC subpopulations such as CDC patients should be further investigated [61].

7.11.4 Targeted Therapy

Staehler et al. (2008) reported no response to sunitinib in two patients with mCDC [62]. Miyake et al. (2011) presented a case report of partial response of mCDC after sunitinib therapy [63]. Procopio et al. (2012) reported a series of seven patients receiving targeted therapies (sorafenib, temsirolimus and sunitinib). Two patients experienced a period of disease stabilization with an overall survival time of 49 (sorafenib followed by sunitinib) and 19 months (temsirolimus followed by sunitinib), respectively [64]. Two case reports showed response of mCDC after sorafenib therapy [65, 66].

There is no evidence to support the efficacy of targeted therapy, such as sunitinib and sorafenib beyond small series. Prospectively investigating the role of targeted therapy in the management of mCDC would be valuable.

Table 7.2 summarizes the main studies of therapeutic regimens for CDC.

7.12 Prognosis and Predictive Factors

Three multi-institutional retrospective studies were published from the United States [10], Europe [12] and Japan [14] showing that CDC presents usually at an advanced stage and has a poor prognosis, due to the frequent finding of distant metastases at the time of diagnosis [7, 10, 13, 14, 17, 26–28, 53, 67–72].

Table 7.2 Summary of the main studies of therapeutic regimens for CDC

References	Therapeutic regimen	Outcome
Tokuda et al. [14]	Immunotherapy Chemotherapy	No responses 1 PR to gemcitabine/carboplatin 1-, 3-, 5- and 10-year disease-specific survival 69.0%, 45.3%, 34.3% and 13.7%
Oudard et al. [15]	Gemcitabine/platinum	Objective response rate 26% (95% CI 8–44) 1 CR, 5 PR, 10 SD and 7 PD Median OS: 10.5 mo (95% CI 3.8–17.1) Median PFS: 7.1 mo (95% CI 3.0–11.3)
Procopio et al. [64]	4 patients on sorafenib 1 patient on sunitinib 2 patients on temsirolimus	Long-lasting disease control 1 patient had OS of 49 mo (sorafenib followed by sunitinib) 1 patient had OS of 19 mo (temsirolimus followed by sunitinib)
Pécuchet et al. [57]	Bevacizumab + gemcitabine + platinum salt	3 PR and 2 SD Median OS: 27.8 mo (95% CI 12.4–unreached) Median PFS: 15.1 mo (95% CI 5.6–20.4)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *OS* overall survival, *PFS* progression-free survival, *mo* months

Early diagnosis is therefore important and may increase survival. A high frequency of local recurrence is reported, even when a radical nephrectomy has been successfully performed [24].

In the Japanese study, with a series of 81 CDC patients, regional lymph node metastases were detected in 44% of the patients, while 32% of the population had distant metastases at presentation. The 5-year disease-specific survival was 34.3% [14].

In the European multi-institutional surgical series, CDC patients presented with more advanced stage and more aggressive disease compared to clear cell RCC patients. Of all CDC patients, 76% had pT3 disease at nephrectomy versus 37% for those with clear cell RCC. The predominant Fuhrman grades were III (56%) and IV (22%) in CDC patients versus II (42%) and III (28%) for clear cell RCC patients. Of all CDC patients, 19% had distant metastases at nephrectomy compared to 14% of the clear cell RCC patients. After nephrectomy, when 41 CDC cases were matched for grade, tumour size and TNM stages with 105 clear cell RCC controls, no difference in 5-year disease-specific survival was observed (48% and 57%, respectively). An explanation for this paradox cannot be offered readily and may require more information on the tumour biology of CDC [12].

On analysis of the Surveillance, Epidemiology, and End Results (SEER) database for the years 2001–2005, i.e. before the introduction of anti-angiogenic drugs, mortality for CDC (n = 160) was 2.42-fold higher than for clear cell RCC (n = 33,252). The 3-year disease-specific survival rate was 58% and 79% for CDC and clear cell RCC, respectively [10].

In the study by Oudard et al. including 23 patients with mCDC on a GC regimen, 66% of patients died of the disease within 2 years after diagnosis [15]. Recently, a multi-institutional study with 95 CDC patients collected from 16 European and American centres reported a 5-year disease-specific survival of 40.3% with a median follow-up time of 48.1 months. The authors assessed the parameters prognostic for disease-specific mortality: American Society of Anesthesiologists (ASA) score 3–4, tumour size greater than 7 cm, stage M1, Fuhrman grade 3–4 and lymphovascular invasion. Based on these parameters, patients were divided into 26 (27%) at low-risk (0–2 points), 13 (14%) at intermediate-risk (3 points) and 56 patients (59%) at high-risk group (4–7 points) with a 5-year disease-specific survival of 96%, 62% and 8%, respectively ($P < 0.001$). A subset of low-risk patients has excellent survival when histopathological parameters in a highly accurate risk model were used to stratify the patients [13]. A recent multi-institutional study that examined the treatment results in 35 CDC patients showed seven long-term survivors. Long-term survivors were in stages I–III and those who received palliative treatment after a relapse. The treatments administered to these patients included targeted therapy as well as immunotherapy and chemotherapy. Therefore, additional research on predictive markers, by which the outcomes of prognosis and therapy as well as their clinical features can be predicted, is needed [53].

Conclusion

CDC is a rare and aggressive subtype of RCC arising from the principal cells of the collecting duct epithelium. It presents at an advanced stage and has an extremely poor prognosis. Imaging features of CDC are non-specific.

Light microscopy findings are typically described as a cytologically high grade, tubular or tubulopapillary growing carcinoma within a desmoplastic stroma. Histological and immunohistochemical analyses, together with clinical data, are critical in establishing an accurate diagnosis of CDC and for distinguishing this tumour from other subtypes of RCC.

Understanding the molecular pathogenesis of CDC will play a key role in the future subclassification of this unique tumour. Most of the CDC patients receive surgical treatment although evidence for the role of surgery is lacking in the literature. Several other treatments including chemotherapy, radiotherapy and immunotherapy have been considered but have a poor response. Given the lack of any other beneficial agent, a GC regimen should be considered the standard of care for first-line systemic treatment of mCDC patients. The role of targeted therapy in the management of CDC has not been established because of the limited data to date.

Early diagnosis, additional research on predictive markers and prospective multi-institutional studies to investigate treatments of CDC will be necessary to improve the outcome of these patients.

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