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# Collecting Ducts Carcinoma Approach in the New Era of Targeted and Immunotherapy

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## Abstract

Collecting duct carcinoma (CDC), or Bellini duct carcinoma, is a rare and aggressive subtype of renal cell carcinoma, accounting for 0.2% - 1% of cases. It often presents at an advanced stage with nonspecific symptoms, requiring histopathology for diagnosis. Surgery remains the standard of care for localized disease, serving both diagnostic and therapeutic purposes, though adjuvant chemotherapy has shown limited efficacy. In metastatic CDC, the gemcitabine-cisplatin regimen is commonly used due to its resemblance to urothelial cancer and supportive data from prospective studies. Newer therapies offer promise in advanced cases. Immune checkpoint inhibitors, such as nivolumab alone or with ipilimumab, have shown benefits in patients with high PD-L1 expression. Targeted therapies like cabozantinib demonstrated efficacy and safety as first-line treatments in phase II trials, while sunitinib and sorafenib have shown responses in various case reports and cohorts. However, combining chemotherapy with bevacizumab did not improve outcomes in phase II trials. Despite therapeutic advances in urothelial cancers and clear cell renal tumors, the CDC entity remains a challenging malignancy, emphasizing the need for continued research to understand the true efficacy of treatment and to prolong survival in advanced disease.

## Keywords

Collecting Duct Carcinoma, Bellini Tumor, Nephrectomy, Chemotherapy, Targeted Therapy, Immunotherapy

## 1. Introduction

Collecting duct carcinoma (CDC) of the kidney, known also as Bellini tumor, is a rare histological type of renal cell carcinoma (RCC) with distinctive clinical and

histopathological features. Unlike most renal cell carcinoma tumors that occur in the epithelial cells of the proximal tubules, collecting duct carcinoma originates in the distal collecting ducts. Formerly known as carcinoma of the collecting ducts of Bellini or Bellini duct carcinoma, it was first recognized by Fleming and Lewi in 1986 as a distinct subtype of RCC [1]. 0.2% - 1% of all RCC are CDCs with a male predominance of 2:1 [2]. It presents generally at an advanced stage since 50% are diagnosed at stage IV, with symptoms such as flank pain, hematuria, lower urinary tract symptoms, and weight loss. Patients with CDC are younger than those with RCC on diagnosis with a mean age at diagnosis 59 years [3]. It is an aggressive disease with a high incidence of early mortality leading to 60% - 70% death within 3 years of diagnosis [4]. Metastatic sites of CDC are the lungs, liver, lymph nodes (retroperitoneal), adrenals and bones (vertebrae). Uncommon sites such as the heart have been reported [5].

## 2. Diagnosis and Characteristics

Collecting duct carcinomas tend to have special characteristics on CT like a medullary location, a heterogeneous and weak enhancement of the lesion, a renal sinus involvement, an infiltrative growth, maintained renal contour, and a cystic component. It often spares the glomerula, with ill-defined margins and frequent infiltration into perinephric tissues. However, these findings are not specific, and histopathology is mandatory for diagnosis.

Microscopically, the characteristics of CDC are outlined in six criteria established by the Vancouver Classification of Renal Neoplasia, proposed by the International Society of Urological Pathology (ISUP) in 2013. These criteria were then incorporated into the fourth edition of the World Health Organization (WHO) Classification of Tumors of the Urinary System. The criteria include: 1—at least partial involvement of the medullary region, 2—a predominantly tubular morphology, 3—desmoplastic stromal reaction, 4—high-grade cytological features, 5—an infiltrative growth pattern, and 6—the exclusion of other typical RCC subtypes or invasive urothelial carcinoma [6]. Despite these defined features, CDC shares significant morphological similarities with other high-grade carcinomas that affect the renal medulla. These overlapping entities include high-grade urothelial carcinoma, renal medullary carcinoma (RMC), and newly recognized types such as fumarate hydratase (FH)-deficient RCC and ALK-rearranged RCC. Consequently, the diagnosis of CDC is often one of exclusion. In fact, imaging characteristics and presentation could be suggestive of collecting duct carcinoma, but surgery and histopathology remain crucial for diagnosis.

CDC has the same staging system as RCC, based on AJCC 8$^{th}$ edition of 2018, where staging is determined by tumor size, extent, and spread [7] (**Table 1**). Although classified and staged as part of RCC, CDC is thought to originate from the collecting duct epithelium, which is derived from the mesonephros. In contrast, other RCC subtypes arise from the kidney's remaining tubular structures, which develop from the metanephric blastema. The mesonephric (Wolffian) duct

undergoes branching to form the ureter, renal pelvis, calyces, and eventually, the collecting ducts. In the medulla, the collecting tubules of each renal pyramid merge into a central duct (the duct of Bellini) that opens at the papillary tip [8]. This unique origin may explain CDC's aggressive behavior, resistance to treatment, and rapid progression compared to other RCC subtypes, highlighting the need for distinct therapeutic strategies.

**Table 1.** Staging of renal cell carcinoma, according to AJCC 8th edition.

| Stage | Tumor (T) | Nodes (N) | Metastasis (M) |
|---|---|---|---|
| Stage I | T1 (Tumor ≤7 cm, confined to the kidney) | N0 (No regional lymph nodes) | M0 (No distant metastasis) |
| Stage II | T2 (Tumor >7 cm, confined to the kidney) | N0 | M0 |
| Stage III | T3 (Tumor extends into major veins or perinephric tissues but not beyond Gerota's fascia) OR T1-T3 | N1 (Metastasis in regional lymph nodes) | M0 |
| Stage IV | T4 (Tumor invades beyond Gerota's fascia or adjacent organs) OR any T | Any N | M1 (Distant metastasis present) |

## 3. Treatment

### 3.1. Surgery

The treatment guidelines for localized CDC align with those for localized RCC. Small tumors are typically managed with partial nephrectomies, while larger tumors often require radical or open nephrectomies. For patients who are not surgical candidates, options such as radiofrequency ablation, stereotactic body radiotherapy (SBRT), microwave ablation, or active surveillance may be considered, particularly for frail individuals with limited life expectancy [7]. However, localized disease of CDC remains an uncommon entity due to the tumor aggressiveness and progression.

Nephrectomy remains the number one treating modality based on the literature with many isolated cases of early disease having a long-term survival reported in the literature [9]-[11]. It is important to note that almost all localized collecting duct tumors are diagnosed based on pathology after nephrectomy. The nephrectomy being diagnostic and therapeutic in these cases. The type of surgery when treating these tumors remains unknown due to limited and insufficient data. However, there is a consensus that given the aggressive nature of this tumor, the most radical technique possible should be always considered (radical nephrectomy plus lymphadenectomy) [12].

- While the optimal type of nephrectomy remains unclear due to limited data, surgery remains the primary treatment for localized CDC, fulfilling both

diagnostic and therapeutic roles.

### 3.2. Adjuvant Chemotherapy

The effectiveness of adjuvant treatment after nephrectomy, for most cases of CDC reported in the literature, remains unsatisfactory. While some patients have undergone adjuvant systemic therapy, the outcomes have demonstrated limited efficacy, with survival times ranging from 4 to 7 months. In fact, Staehler *et al.* reported Two patients with CDC who underwent an adjuvant regimen of gemcitabine and cisplatin for two cycles following radical nephrectomy and lymphadenectomy. Local recurrence occurred subsequently in both cases. Additionally, sunitinib, used after complete resection of the relapse, failed to produce any clinical benefit [13].

- Adjuvant treatment after nephrectomy for CDC has shown limited efficacy, with survival times of 4 to 7 months, as reported cases, including those treated with gemcitabine-cisplatin, and sunitinib, have experienced recurrence and lack of clinical benefit.

### 3.3. Chemotherapy for Advanced and Metastatic CDC

The ESMO approach of advanced CDC is similar to others non-clear-cell and non-papillary RCC. As consequence, enrolment into clinical trials is strongly recommended for treatment of advanced CDC, since any available evidence is primarily drawn from small prospective studies and subgroup analyses of larger trials. The ESMO recommends four regimens: cisplatin-based chemotherapy, Sunitinib, Pazopanib and Cabozantinib with these degrees of evidence II C, V C, V C and II C respectively [7].

Data favoring cytoreductive nephrectomy (CN) and systemic therapy over systemic therapy (ST) alone is present in the literature. Panunzio *et al.* demonstrated that with a median overall survival of 4.0 months for CN alone vs. 5.5 months for ST alone vs. 9.0 months for combination of both CN + ST [14]. Class, dose, and duration of administered systemic therapy were unavailable.

Extrapolated from advanced bladder cancer therapy, the Gemcitabine-Cisplatin (GC) regimen remains nowadays, the first-line systemic treatment in metastatic CDC as no other specific chemotherapeutic agent has demonstrated a beneficial effect. Oudard *et al.* succeeded in confirming the effectiveness of the GC regimen in treating metastatic CDC. Participants received 21-day cycles of gemcitabine 1250 mg/m$^2$ on days 1 and 8, plus cisplatin 70 mg/m$^2$ or carboplatin on day 1, depending on renal function. The study showed a 26% (95% CI: 8% - 44%) objective response rate, almost similar to responses seen in urothelial carcinoma. Notably, 87% of patients had undergone nephrectomy before starting chemotherapy. Progression-free survival (PFS) was 7.1 months, and overall survival (OS) was 10.5 months. GC was relatively safe, with only mild-to-moderate toxicities (Grade 1 - 2) reported and no treatment discontinuation due to side effects [15]. In the McMaster series, cytoreductive nephrectomy was performed in 4 out of 6 patients.

Among 2 patients who received MVAC therapy (methotrexate, vinblastine, doxorubicin, and cisplatin), no response was observed. While no major therapeutic complications were reported, median survival was 11 months (range: 10 - 33 months) [16]. Case reports have also highlighted responses to paclitaxel [17], and paclitaxel and carboplatin [11] [18].

- The Gemcitabine-Cisplatin (GC) regimen, extrapolated from advanced bladder cancer therapy, remains the first-line treatment for metastatic CDC, demonstrating a 26% response rate, a median overall survival of 10.5 months, and manageable toxicity, while alternative therapies like MVAC and paclitaxel-based regimens have shown limited or variable efficacy.

### 3.4. Immunotherapy

Two old retrospective studies reported limited benefit of immunotherapy in treating metastatic CDC. In a Japanese study by Tokuda *et al.*, 34 patients with CDC received interferon-alpha (IFN-$\alpha$), interferon-gamma (IFN-$\gamma$), or interleukin-2 (IL-2), but no responses were observed. The authors noted only one partial response to gemcitabine-cisplatin after the failure of immunotherapy. Similarly, Motzer *et al.* reported no response among 15 patients treated with IFN-$\alpha$ or IL-2 for metastatic CDC. Based on these findings, immunotherapy appears to offer no significant benefit in this rare and aggressive cancer [4] [19].

Concerning the new generation immunotherapy such as immune check-point inhibitors, nivolumab alone or in combination with ipilimumab have been used in several case studies with promising outcome [20]-[22]. Mizutani *et al.* and Yasuoka S *et al.* reported two cases that showed efficacy of Nivolumab in metastatic CDC with high PDL1 expression and progression on prior therapies with chemotherapy and targeted therapy [21] [22]. Fuu *et al.* described a case of CDC with high PD-L1 expression that received ipilimumab and nivolumab after progression. Despite developing interstitial pneumonitis due to treatment and receiving only one dose of it, the patient achieved complete response after three years of follow-up [20]. Watanabe *et al.* reported a case of CDC with metastases involving the paraaortic and bilateral external iliac lymph nodes on presentation. Cytoreductive open nephrectomy without lymphadenectomy was done and treatment with Ipilimumab and Nivolumab was given. Complete response was achieved at 6 months and lymphadenopathies shrunk to less than 1 cm. No data was given concerning the PD-L1 expression [23].

- While older retrospective studies showed no significant benefit of immunotherapy in metastatic CDC, newer immune checkpoint inhibitors like nivolumab, alone or with ipilimumab, have demonstrated promising responses, particularly in cases with high PD-L1 expression, with some achieving complete remission.

### 3.5. Targeted Therapy

The Phase II BONSAI Trial evaluated cabozantinib, a multi-targeted TKI given as

60 mg daily, in 25 patients with metastatic CDC. Among 23 evaluable patients, 3 achieved stable disease, 1 had a confirmed complete response, and 7 showed a partial response, resulting in an objective response rate of 35%. The median progression-free survival was 4 months (95% CI: 3 - 13 months), and the median overall survival was 7 months (95% CI: 3 - 31 months). After 12 months, 10 patients (43%) were still alive, and 5 patients (23%) were continuing treatment. Cabozantinib was generally safe with grade 3 adverse effects being reported such as arterial hypertension, pulmonary thromboembolism, bleeding, and fatigue. There were no permanent discontinuations owing to adverse effects. Four patients required dose reduction to 40 mg, and four a transitory interruption to manage toxic effects [24].

In a systematic review and meta-analysis on systemic therapy in non-clear cell RCC, sunitinib was reported to be less efficient in this histologic type compared to sunitinib used in clear-cell RCC. Non-clear cell RCC included in this study papillary I/II, chromophobe, collecting duct, renal medullary, mucinous tubular, spindle cell, carcinoma associated with neuroblastoma, Xp11 translocation, and unclassified carcinomas. Sarcomatoid variant was considered a high-grade transformation of different subtypes of RCC. Specific data on collecting duct carcinomas was not recorded. The difference in response between clear cell and non-clear cell patients was not noted with Sorafenib which can be due to low number of treated patients with the agent [25].

In a cohort of 333 patients including 7 with metastatic CDC, six patients had nephrectomies, while one was diagnosed through a biopsy due to local tumor extension. All 7 patients were treated with targeted therapies: 4 received sorafenib, 1 received sunitinib, and 2 received temsirolimus. After disease progression, 2 patients were given second-line treatment with sunitinib. Two patients showed disease control with their first treatment: one with sorafenib (33 months) and the other with temsirolimus (6 months). After progression, both received sunitinib as second-line therapy, achieving an additional 10 and 9 months of disease control, with overall survival of 49 and 19 months, respectively. The other five patients, who experienced early progression (3 on sorafenib, 1 on sunitinib, and 1 on temsirolimus), had a survival of only 4 months [26]. Zhao *et al.* reported a case of metastatic CDC treated with nephrectomy followed by GC. After disease progression, sorafenib was initiated, leading to a partial response with over 30% reduction in metastasis size. However, progression was observed 12 months after starting sorafenib [27]. Ansari *et al.* reported a patient with metastatic CDC showing an excellent clinical and radiological response, with progression-free survival exceeding 13 months with sorafenib therapy [28].

- The Phase II BONSAI trial demonstrated cabozantinib's potential in metastatic CDC with a 35% response rate and manageable toxicity, while other targeted therapies like sorafenib, sunitinib, and temsirolimus have shown variable efficacy, with some cases achieving prolonged disease control but overall limited survival benefits.

### 3.6. Combination of Chemotherapy and Targeted Therapy

In a Phase II trial, the combination of oral sorafenib with gemcitabine and cisplatin was evaluated in 26 metastatic CDC patients. Most patients had undergone nephrectomy prior to treatment. After four cycles of combination therapy, patients with complete response, partial response, or stable disease received maintenance sorafenib until disease progression or unacceptable toxicity. The treatment showed promising results, with a median progression-free survival of 8.8 months and a median overall survival of 12.5 months. The therapy was generally safe, with most side effects being mild to moderate and manageable through dose adjustments or supportive care. Myelosuppression and gastrointestinal issues were the most common side effects, and no treatment-related deaths were reported. Grade 3 - 4 toxicities such as leucopenia, thrombocytopenia and anaemia were also recorded [29].

The combination of chemotherapy and Bevacizumab was also investigated in the setting of metastatic CDC. Despite small studies reporting positive responses when added to the combination of gemcitabine and cisplatin, larger trials have shown limited benefit [30] [31]. In fact, a small study of five patients with metastatic CDC treated with this combination followed by maintenance bevacizumab reported a median progression-free survival of 15.1 months and overall survival of 27.8 months, with manageable toxicities [30]. However, a phase II trial published in 2023, found no significant benefit from adding bevacizumab to chemotherapy in metastatic renal medullary carcinoma and metastatic CDC, with higher than-expected toxicity [32]. As a result, the addition of bevacizumab to GC regimen is not a standard therapeutic option for metastatic CDC patients.

- A Phase II trial showed promising results for sorafenib combined with gemcitabine and cisplatin in metastatic CDC, with a median overall survival of 12.5 months and manageable toxicity, while bevacizumab added to chemotherapy has shown mixed results, with small studies reporting benefits but larger trials finding limited efficacy and higher toxicity.

## 4. Lessons from Current Approaches of Metastatic CDC

Gemcitabine plus Cisplatin remains the standard of care in managing metastatic CDCs. MVAC regimen could be also offered based on the resemblance that this tumor has with urothelial cancer, although no objective data favors MVAC and adverse effects should be monitored. Adding Sorafenib to GC regimen offers the best combination of treatment to date. A treatment that increases median overall survival to almost one year.

While the double ICIs significantly improved overall survival compared with conventional therapies for intermediate and poor risk metastatic RCC [33], the efficacy of the combination of nivolumab and ipilimumab in metastatic CDCs could be found as individual case reports in the literature [20]-[23]. Therefore, larger studies are needed to evaluate adequately this combination. In parallel, nivolumab was proven efficient in metastatic urothelial cancer when combined

with cisplatin-based chemotherapy [33] rendering worthy to assess this combination in metastatic CDC.

Cabozantinib, has shown benefits in advanced CDC, with outcomes comparable to those seen with the gemcitabine-cisplatin (GC) regimen. However, it does not provide a substantial advantage, and further studies are needed to fully assess the role of TKIs in treating advanced CDC. Additionally, one case report have documented response to dual anti-HER2 therapy in HER2-positive patient, reinforcing the benefit of personalized targeted therapies that could potentially transform the management of metastatic CDC [34].

## 5. Conclusion

CDC is classified as a subtype of RCC based on histology but differs significantly in presentation, imaging features, and prognosis. It is characterized by an aggressive clinical course, poor outcomes, and limited responsiveness to treatment. Surgery remains the standard of care for localized disease, and gemcitabine-cisplatin, extrapolated from metastatic urothelial cancer remains the standard first-line regimen which offers the best responses in advanced cases. Antiangiogenic therapies have not provided a viable solution for this aggressive tumor while tyrosine kinase inhibitors, such as Cabozantinib seem promising, as well as the combination of chemotherapy and Sorafenib. Immunotherapy, such as Nivolumab, could also have an effective role in advanced setting. Knowing that CDC is a rare tumor entity, molecular profiling and subsequent personalized treatment options are frequently emphasized. Nevertheless, future studies should focus on large series combining targeted therapies to chemotherapy and immunotherapy to improve outcomes for these specific patients.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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