# ORIGINAL ARTICLE

# Management of renal collecting duct carcinoma: a systematic review and the McMaster experience

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## ABSTRACT

### Introduction

Collecting duct carcinoma (CDC) is a rare, aggressive form of renal carcinoma that presents at an advanced stage and has a poor prognosis. Little is known concerning the optimal management of CDC. We present the results of a systematic review addressing the management of CDC and the McMaster University CDC series.

### Methods

The MEDLINE, Cochrane Library, and EMBASE databases and conference proceedings were searched to identify studies relating to the management of CDC. Included studies reported on a minimum of 10 subjects receiving a single intervention. Series in which an evaluation of therapeutic effectiveness was not possible were excluded. The McMaster University (Hamilton, Ontario) series of 6 cases of CDC were retrospectively reviewed.

### Results

We identified 3 studies relevant to the management of CDC that included a total of 72 patients. A gemcitabine–cisplatin or –carboplatin regimen resulted in a 26% objective response rate in 23 patients with metastatic CDC. Two additional studies indicated that 49 patients treated with immunotherapy achieved no response. In the McMaster series, cytoreductive nephrectomy was performed in 4 of 6 patients. In 2 patients, MVAC therapy (methotrexate–vinblastine–doxorubicin–cisplatin) achieved no response. No significant therapeutic complications occurred, but survival was poor (median: 11 months; range: 10–33 months).

### Conclusions

Our review and clinical experience suggest that the current standard of care for metastatic CDC is a gemcitabine–cisplatin regimen.

## KEY WORDS

Collecting duct carcinoma, Bellini duct carcinoma, renal cell carcinoma, cytoreductive nephrectomy, gemcitabine, cisplatin, MVAC

## 1. INTRODUCTION

Collecting duct carcinoma (CDC) or Bellini duct carcinoma is a rare type of renal cell carcinoma (RCC) thought to originate from renal collecting duct epithelium. Three multi-institutional retrospective CDC series including 262 patients were recently published from the United States[1], Europe[2], and Japan[3].

The U.S. population–based series by Wright *et al.* characterized CDC epidemiology in North America (Table I)[1]. Compared with clear cell RCC, CDC is more common in African American and male patients. The median age at diagnosis of 63 years did not differ from that for clear cell RCC. At diagnosis, collecting duct carcinoma was also more commonly locally advanced, metastatic, and poorly differentiated, resulting in worse 1- and 3-year disease-specific survivals.

The European[2] and Japanese[3] series also found that CDC presents at an advanced stage and has a poor prognosis. Additionally, those series indicated that more than two thirds of patients with CDC exhibit locoregional or systemic symptoms on presentation. The most common metastatic sites included regional lymph nodes, lung, bone, and liver[3].

Two retrospective series with a total of 35 patients suggest that several computed tomography findings may predict CDC histology[4,5]. Those findings include medullary location, weak and heterogeneous enhancement, involvement of the renal sinus, infiltrative growth, preserved renal contour, and a cystic component. Nonetheless, the low pre-test probability of CDC and the lack of specificity in the criteria necessitate histopathology for CDC diagnosis.

The major criteria for CDC classification in the World Health Organization's Classification of Tumors include location in a medullary pyramid;

TABLE I    Characteristics of patients with collecting duct carcinoma (CDC) and with clear cell renal cell carcinoma (CCRCC)[1]

| Characteristic[a] | Patient group (%) | |
| --- | --- | --- |
| | CDC (n=160) | CCRCC (n=33,252) |
| Men | 70 | 62 |
| African American | 23 | 9 |
| Locally advanced disease[b] | 28 | 16 |
| Metastatic disease[b] | 28 | 17 |
| Poorly differentiated[b] | 70 | 31 |
| Survival [median (95% CI)][c] | | |
| 1-Year | 70 (62–77) | 87 (86–87) |
| 3-Year | 58 (48–67) | 79 (78–80) |

[a]    Listed characteristics differ significantly ($p < 0.05$).
[b]    At presentation or staging.
[c]    Estimated using the Kaplan–Meier method.

typical histology, with irregular tubular architecture and high nuclear grade; inflammatory desmoplastic stroma with numerous granulocytes; reactivity to antibodies against HMWCK, reactivity with UEA-I, and absence of urothelial carcinoma[6]. Contemporary pathology research has focused on excluding urothelial carcinoma and papillary RCC by immunohistochemical staining for PAX8, p63, E-cadherin, c-Kit, CD10, and others[7,8]. Pathology diagnosis of CDC is complex and, at our institution, warrants specialized review.

Recently published series[1–3] and conventional secondary sources[9] do not provide direction on the appropriate management of CDC. It is for that purpose that we report the results of a systematic review addressing the management of CDC. The McMaster University CDC series is also presented.

## 2.    METHODS

### 2.1    Systematic Review

A systematic literature review was performed to evaluate management options for CDC. Databases searched included Ovid MEDLINE, the Cochrane Library, EMBASE, and the Thomson Reuters Conference Proceedings Citation Index. Search results were filtered by three researchers.

The literature searches were performed on August 1, 2012, and studies with English abstracts from 1980 to August 2012 were included. Table II summarizes the search strategies.

Included studies reported on a minimum of 10 subjects with a histopathologic diagnosis of CDC receiving a single intervention. Series in which an

evaluation of therapeutic effectiveness was not possible were excluded (for example, surgical series with no comparison group). Subgroups within a larger study that fulfilled the inclusion and exclusion criteria were also included.

The primary outcome was response rate (complete or partial, as defined by the study). Secondary outcomes included progression-free survival, overall survival, and toxicity. Also recorded were the study design, number of patients, location of patients, patient and tumour demographics, criteria for diagnosis, and criteria for assessing response. Study quality was evaluated by assigning each study a level of evidence based on the levels of evidence criteria set out by Oxford University's Centre for Evidence-Based Medicine[10]. Search terms, inclusion and exclusion criteria, and outcomes were defined *a priori*.

Figure 1 presents an overview of the systematic review searches.

### 2.2    Case Series

During 2000–2012, 6 patients treated at a single institution (McMaster University, Hamilton, Ontario) received a diagnosis of CDC. Patient information was retrospectively extracted from the office charts for those patients and from regionally-linked electronic medical records. Extracted data included presenting history, staging, treatment, pathology, post-treatment course, and survival. Cytoreductive nephrectomy was defined as nephrectomy performed after a diagnosis of metastatic disease.

## 3.    RESULTS

### 3.1    Systematic Review

We identified three studies that met our specified inclusion and exclusion criteria. Excluded studies were either isolated case reports, small surgical series, or articles not relevant to the search.

#### 3.1.1    *Gemcitabine and Cisplatin*
Oudard *et al.* published a prospective multicentre phase II study evaluating the effect of gemcitabine and either cisplatin or carboplatin (GC) on CDC[11] (level of evidence: 2b). This study, conducted at 6 French institutions, reported on patients with metastatic CDC, confirmed by centralized histopathology review, who had received no systemic treatment or radiotherapy in the 4 weeks before inclusion. Median patient age was 65 years (range: 18–74 years), and 87% had previously undergone nephrectomy. In 96% of the patients, Eastern Cooperative Oncology Group performance status was 2 or less.

Participants received 21-day cycles of gemcitabine 1250 mg/m$^2$ on days 1 and 8, plus cisplatin or carboplatin 70 mg/m$^2$ (based on renal function)

TABLE II  Literature search strategies

| Step | MEDLINE search term | Results | EMBASE search term | Results |
|---|---|---|---|---|
| 1 | exp renal neoplasms/ | 50,116 | Collecting duct.mp. | 4,918 |
| 2 | Collecting duct.mp. | 4,854 | Bellini duct.mp. | 89 |
| 3 | Bellini duct.mp. | 65 | (treatment or chemotherapy or radiotherapy or management or MVAC or methotrexate or vinblastine or Adriamycin or cisplatin or gemcitabine or carboplatin or Taxol or doxorubicin or ifosfamide or paclitaxel or cisplatin or ITP or monoclonal antibody or immunotherapy or tyrosine kinase inhibitor or VEGF inhibitor or pazopanib or mTOR inhibitor or temsirolimus or everolimus or EGFR inhibitor or sunitinib or sorafenib or IL2 or interleukin 2 or targeted therapy or molecular therapy or cytoreductive nephrectomy or radical nephrectomy or partial nephrectomy or nephrectomy or metastectomy or surgery or resection).mp. | 5,477,368 |
| 4 | 1 and (2 or 3) | 362 | exp kidney carcinoma/ | 31,931 |
| 5 | (treatment or chemotherapy or radiotherapy or management or MVAC or methotrexate or vinblastine or Adriamycin or cisplatin or gemcitabine or carboplatin or Taxol or doxorubicin or ifosfamide or paclitaxel or cisplatin or ITP or monoclonal antibody or immunotherapy or tyrosine kinase inhibitor or VEGF inhibitor or pazopanib or mTOR inhibitor or temsirolimus or everolimus or EGFR inhibitor or sunitinib or sorafenib or IL2 or interleukin 2 or targeted therapy or molecular therapy or cytoreductive nephrectomy or radical nephrectomy or partial nephrectomy or nephrectomy or metastectomy or surgery or resection).mp. | 3,747,748 | 4 and (1 or 2) | 382 |
| 6 | 4 and 5 | 141 | 3 and 5 | 202 |
| 7 | limit 6 to yr="1980–Current" | 141 | limit 6 to (human and yr="1980–Current") | 190 |
| 8 | limit 7 to humans | 140 | | |

on day 1 ($n = 23$ gemcitabine, $n = 12$ cisplatin, $n = 6$ carboplatin, and $n = 5$ cisplatin then carboplatin). Participants underwent a median of 6 cycles of treatment (range: 1–8 cycles).

In the study, participating patients demonstrated a 26% partial or complete response rate [95% confidence interval (CI): 8%–44%], with 1 complete response. Another 10 patients (44%) experienced disease stabilization, and 7 had progressive disease (30%). Responses were assessed using radiologic guidelines from the European Organization for Research and Treatment of Cancer, the U.S. National Cancer Institute, and the National Cancer Institute of Canada[12]. Progression-free survival was 7.1 months (95% CI: 3.0–11.3 months), and overall survival was 10.5 months (95% CI: 3.8–17.1 months).

In terms of toxicity, no treatment-related deaths occurred. Grades 3 and 4 leukopenia, granulocytopenia, anemia, and thrombocytopenia were experienced by 35%, 52%, 44%, and 26% of patients respectively. Rates of grade 1 or 2 creatinine or liver enzyme rise, neuropathy, and anorexia were less than 10%. One patient experienced grade 3 hypercalcemia.

### 3.1.2  Immunotherapy

Tokuda et al.[3] published a retrospective series based on a multi-institutional survey (66 Japanese institutions—level of evidence: 4). In a subpopulation of that series, immunotherapy was used [interferon (IFN-α, IFN-γ), or interleukin 2 (IL-2), $n = 34$]. The series had central histopathology confirmation by 2 pathologists. In the 34 patients treated with immunotherapy, no responses were observed. Response criteria and baseline characteristics, toxicity, and survival of the subpopulation were not reported. The authors anecdotally mentioned 1 tentative partial response to GC therapy after failure of immunotherapy.

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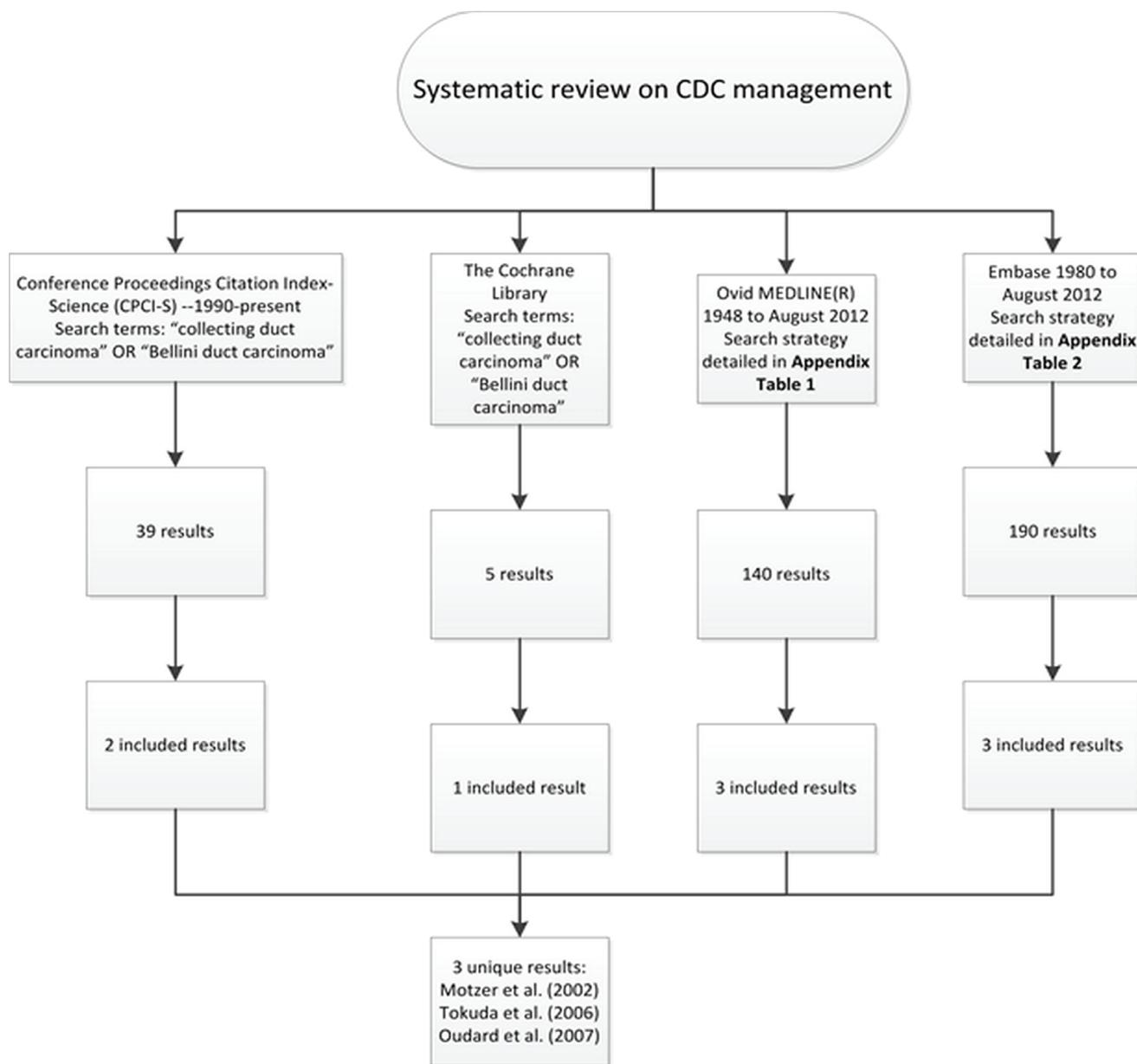
*FIGURE* 1  *Overview of the systematic review search methodology. Study selection criteria were a minimum of 10 subjects, a histopathologic diagnosis of collecting duct carcinoma (CDC), and administration of a single intervention. Series in which an evaluation of therapeutic effectiveness was not possible were excluded (surgical series with no comparison group, for instance).*

Motzer *et al.*[13] also published a retrospective review for a single U.S. centre (level of evidence: 4). Patients had metastatic disease and a pathology finding of CDC or medullary carcinoma. In a subpopulation of these patients, IFN-α or IL-2 (*n* = 15) was used. No responses to immunotherapy were observed. Response criteria and baseline characteristics, toxicity, and survival were not reported for the subpopulation. The authors anecdotally mentioned a 5-month partial response to GC in their series.

## 3.2 Case Series

In our institutional series, patients ranged in age from 61 to 72 years, and all presented symptomatically with flank pain, hematuria, lower urinary tract symptoms, and weight loss. Table III summarizes individual patient details. Primary tumours ranged in size from 4 cm to 12 cm. Local invasion, lymphadenopathy, or distant metastases were present in all cases. Metastatic sites included

TABLE III   Patient information

| Pt ID | Age | Sex | Presenting history | Management | Survival (months) |
|---|---|---|---|---|---|
| 1 | 64 | Female | Lower urinary tract symptoms, flank pain, 4.5-kg weight loss, 30 pack–year smoking history | Cytoreductive nephrectomy; unfit for chemotherapy | 33 |
| 2 | 61 | Male | Gross hematuria and flank pain, nonsmoker | Initial nephrectomy aborted because of lymphadenopathy; unresponsive to 4 cycles of MVAC followed by cytoreductive nephrectomy | 11 |
| 3 | 65 | Female | Gross hematuria, 40 pack–year smoking history | Unresponsive to 3 cycles of MVAC | 19 |
| 4 | 70 | Male | Declining performance status, weight loss | Performance status too low for chemotherapy | Lost to follow-up |
| 5 | 69 | Male | Not available | Cytoreductive nephrectomy | 11 |
| 6 | 72 | Male | Lower urinary tract symptoms, no hematuria or flank pain, smoking history | Cytoreductive (partial) nephrectomy (horseshoe kidney) | 10 |

Pt = patient; MVAC = methotrexate–vinblastine–doxorubicin–cisplatin chemotherapy.

the lumbar vertebrae, lungs, liver, retroperitoneal lymph nodes, and adrenals. Table IV summarizes individual tumour characteristics.

Cytoreductive nephrectomy was performed in 4 cases (patients 1, 2, 5, and 6). Patients 2 and 3 received MVAC chemotherapy, although with no apparent response. Chemotherapy was considered in all other patients, but was not administered because of performance status and comorbidities. No complications requiring hospitalization and no deaths from surgery or chemotherapy occurred. Palliative radiotherapy was administered to patient 1 with no apparent symptomatic response, but in patient 2, palliative radiotherapy was moderately effective for pain control.

Histology diagnosis based on a combination of hematoxylin and eosin morphology and immunohistochemical profile was obtained in all cases (Table IV). A selection of slides obtained from our patients illustrate the unique histology of CDC (Figure 2). Staging was clinical in patients 3 and 4 because they did not undergo nephrectomy.

Median survival was 11 months (range: 10–33 months). All deaths were attributed to complications of advanced disease. Patient 4 was lost to follow-up.

## 4. DISCUSSION

### 4.1 Localized CDC

Localized CDC is an uncommon entity[1–3]. No studies encountered in our review addressed the management of localized CDC. Long-term survival has been reported in isolated cases with resected localized disease[15–17]. The role of adjuvant or neoadjuvant therapies is not known.

### 4.2 Non-localized CDC

#### 4.2.1   Surgery
Almost all reported patients with CDC have undergone surgery[1–3,11] and are diagnosed with CDC only after a histopathology examination. To illustrate this point, 87% of patients in the study by Oudard et al. underwent prior cytoreductive nephrectomy. Should CDC be diagnosed on biopsy, evidence for the role of surgery is lacking in the literature. Patients selected for cytoreductive nephrectomy certainly experience improved survival, likely because of selection biases[18]. Differences in tumour biology suggest that trials demonstrating a benefit for cytoreductive nephrectomy in clear cell RCC are not applicable[19–22].

TABLE IV  Tumour information

| Pt ID | Primary tumour size (cm) | Distant metastatic sites (clinical) | TNM stage[a] | Immunohistochemistry |
|---|---|---|---|---|
| 1 | 4 | Lung, vertebral | pT3a (perirenal and hilar fat), N1, M1 | Not available |
| 2 | 7 | Bilateral adrenal | pT4 (splenic invasion), N1, M1 | Positive: CK19, HMW-CK, EMA, vimentin, CK7 Negative: CD10, p63 |
| 3 | 12 | Lung, bilateral | cT3b (IVC extension) possible cT4, N1, M1 | Positive: CK7, CK5/6, p63 Focally positive: MOC31, vimentin, CD10 Negative: CD20 |
| 4 | 11 | Adrenal, liver, lung, vertebral | cT4, N1, M1 | Positive: AE1/AE3, CAM5.2, 34BE12, CK7, CK10 Negative: CK20, PSA, PAP, EMA, vimentin, TTF-1 |
| 5 | 4 | None | pT1, N1, M0 | Not available |
| 6 | 5 | Liver | pT3, N0, M1, R1 mixed Fuhrman 3 CCRCC and CDC | Positive: CK7 |

[a]  According to the *AJCC Cancer Staging Manual*[14].

Pt = patient; IVC = inferior vena cava; CCRCC = clear cell renal cell carcinoma; CDC = collecting duct carcinoma.

It is important to note that the invasive nature of CDC tumours, combined with the poor preoperative performance status of CDC patients, results in an elevated rate of perioperative morbidity and mortality. For example, Mejean *et al.*[23] reported 3 perioperative deaths in their series of 10 patients undergoing surgery for CDC. Surgical complications and recovery may also delay or prevent a patient from receiving systemic therapy[11]. Accordingly, surgical therapy for known CDC must be individualized.
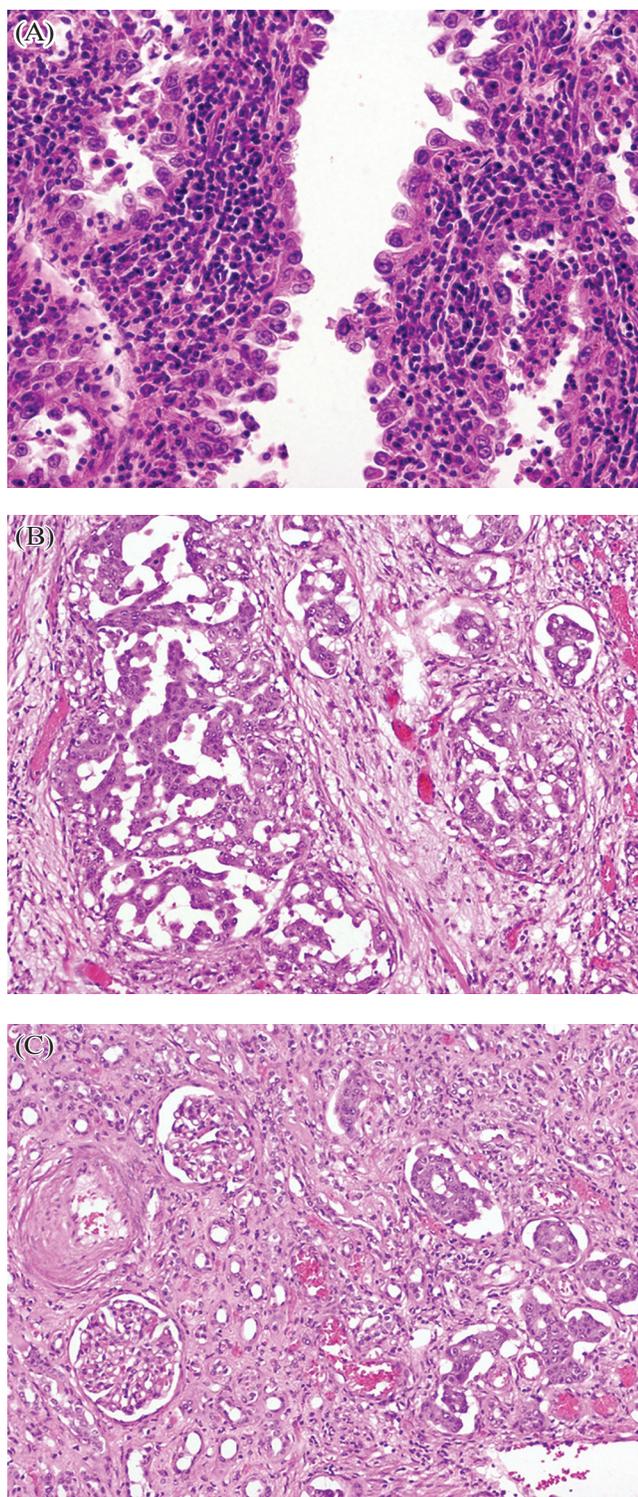
### 4.2.2  Cytotoxic Chemotherapy

Oudard *et al.* demonstrated the effectiveness of a GC regimen in inducing a 26% (95% CI: 8%–44%) objective response rate in CDC. Interestingly, that rate is similar to the rate in urothelial carcinoma, in which a GC regimen is a standard of care in metastatic or invasive disease[24,25]. This trial by Oudard *et al.* is the only one identified in our review that provided evidence of CDC responsiveness to a cytotoxic agent. Given the lack of any other beneficial agent, a GC regimen should be considered the standard of care for first-line systemic treatment of metastatic CDC.

The toxicity of the GC regimen is improved compared with that for traditional MVAC therapy[25]. In their trial, Oudard *et al.* primarily observed hematologic toxicity: grades 3–4 neutropenia and thrombocytopenia were observed in 52% and 43% of patients respectively. No treatment-related deaths occurred.

This uncontrolled phase II study by Oudard *et al.* is limited in several ways. It enrolled 23 patients, falling short of the stated goal of 40 patients. Of the 23 patients, 87% underwent cytoreductive nephrectomy, and thus it is hard to know how the trial findings generalize to patients who have not undergone surgery. Only 52% of the patients had sufficient renal function to complete therapy with cisplatin. Although chemotherapy type (carboplatin, cisplatin, or cisplatin switched to carboplatin) was not a significant predictor of survival on univariate Cox regression, the small number of participants limits that analysis. Furthermore, although the median number of chemotherapy cycles was 6, the range was 1–8 cycles, and how that variation may have affected survival or which factors may have led to the heterogeneity is unknown. As previously mentioned, 87% of the patients in the trial were diagnosed after nephrectomy, and thus it is uncertain how the results apply to patients diagnosed on biopsy. Similarly, 96% of patients had an Eastern Cooperative Oncology Group performance status of 2 or less, which also is a pivotal factor in deciding on cytotoxic therapy.

Despite those limitations, the Oudard *et al.* trial stands as important hypothesis-generating work, and future phase III studies might choose to focus on evaluating other cytotoxic urothelial carcinoma regimens in comparison with GC. Chemosensitivity of CDC cell lines to topoisomerase inhibitors such as doxorubicin has been described[26]. Case reports have also reported responses to MVAC[27,28], paclitaxel[29], and paclitaxel and carboplatin[30,31]. A phase I study documented a response of metastatic CDC to AQ4N, a novel topoisomerase II inhibitor[32].

### 4.2.3    Immunotherapy

Although reports of a response of metastatic CDC to immunotherapy have been published[33,34], our review indicates that immunotherapy (IFN-α, IFN-γ, and IL-2) is not effective in treating metastatic CDC. That conclusion is based on two retrospective series with a total of 49 patients treated with immunotherapy in whom no responses were documented[3,13]. Although details of the specific treatment regimens used were limited (as were response criteria, survival, toxicity, and baseline patient characteristics), the complete lack of effectiveness in these studies was large and homogeneous.

### 4.2.4    Targeted Therapy

Outside of small series or case reports, no evidence supports the efficacy of targeted therapy such as sunitinib or sorafenib for CDC. Procopio *et al.*[35] recently reported a series of 7 patients receiving targeted therapies. Two patients experienced periods of disease stabilization and overall survivals of 49 months (sorafenib, then sunitinib) and 19 months (temsirolimus, then sunitinib). Our review also identified three isolated reports. Staehler *et al.*[36] reported a lack of response to sunitinib in 2 patients with metastatic CDC. Miyake *et al.*[37] reported a contribution of sunitinib to a slight decrease in metastatic tumour burden that fell short of a partial response. Finally, Ansari *et al.*[38] reported a response, with minimal side effects, to sorafenib in a patient with metastatic CDC.

These few positive reports and the current dismal prognosis of CDC indicate that targeted therapy is an important area for future investigation. Accordingly, several trials are under way to evaluate the role of targeted therapies in non-clear cell RCC (search for NCT00465179, NCT01185366, and NCT01219751 at http://clinicaltrials.gov/).

### 4.3 Case Series

The patients in our institutional series reflect many characteristics previously described for CDC. All patients were symptomatic at presentation, with classic symptoms of flank pain or gross hematuria[3]. Presence of flank pain at CDC presentation is ascribed to the infiltrative nature and regional lymphadenopathy of even small CDC tumours, such as the 3.6-cm



FIGURE 2    *Collecting duct carcinoma. (A) Hobnail neoplastic cells with high-grade nuclei (centrally) resting on stroma with inflammatory cells. (B) Tumour cells in large nests and some* in situ *within the collecting ducts. (C) On the left, normal renal parenchyma is visible; on the right* in situ *neoplastic cells are lining the collecting ducts. All images: hematoxylin and eosin stain, 20× original magnification.*

pT3aN1M1 tumour in patient 1. Gross hematuria may be more likely in CDC because of its central location, allowing for direct access to the collecting system.

Patients were diagnosed in about their 6th decade and had advanced staging at presentation, as in other reported series[1]. Interestingly, 2 patients in our series had adrenal metastases, a site not commonly reported for CDC metastasis[3]. The poor prognosis reported in several series also held true for our patients, who had a median survival of 11 months[1–3]. Histopathology diagnosis of CDC in our series was complex and required specialized review. Discussion of CDC histopathology is beyond the scope of the present paper and is reviewed elsewhere[6,7].

Surgical treatment for CDC patients in the present series was individualized. Patients 1, 2, 5, and 6 received cytoreductive nephrectomy. Patient 1 had a small tumour, limited evidence of metastasis, a high performance status, and a diagnosis of CDC that was not known preoperatively. Patient 2 had an invasive tumour, but was thought to be able to tolerate surgery; he had a decent performance status after MVAC therapy and a preference for surgery. Patient 5 had a small tumour and, preoperatively, was presumed to have localized non-CDC disease. Patient 6 was thought to have non-CDC organ-confined disease until the final histopathology report confirmed CDC elements, with local invasion and positive margins. Additionally, hepatic nodules in patient 6 may have been CDC in origin. Because of persistent hematuria, palliative nephrectomy was also offered to patient 3, but the procedure was not performed because the hematuria eventually ceased.

In keeping with the recent study by Oudard *et al.*[11], CDC tumours may be treated systemically with cytotoxic therapy, as in urothelial carcinoma. Accordingly, patients 2 and 3 received MVAC, a standard of care in metastatic urothelial carcinoma[39,40]. The remaining patients would also have received MVAC, except that patients 1, 5, and 6 were unfit for systemic therapy, and patient 4 was noncompliant and lost to follow-up. No responses were observed, but that result is not unexpected given that 17 of 23 patients in the Oudard *et al.* trial did not respond to GC[11]. In our series, MVAC was used in preference to GC because treatment occurred before acceptance of equivalent survival and lower toxicity with GC compared with MVAC in urothelial carcinoma[24,25].

### 4.4 Limitations of Our Review

The present systematic review is limited by several factors. First, only English-language studies after 1980 were searched, a limitation necessary for practical reasons. Similarly, a minimum sample size of 10 patients was chosen, because that study size was thought to be the minimum needed to appropriately observe responses and toxicities in a consecutive series.

For a study to be included in the review, we also required that an objective outcome be measured. This specification was meant to ensure that studies documenting therapeutic efficacy (or lack thereof) could form the basis of clinical decisions. Those criteria are clearly biased against observational surgical case series because no comparator group is available. However, some of the excluded studies are still relevant in the management of CDC, and so they were included in the discussion.

### 4.5 Quality of Available Evidence

Because of the rarity of CDC, the overall quality of the available evidence was fairly poor. The study by Oudard *et al.*[11] was the highest quality study, in that it was a prospective phase II trial with central histopathology review (level of evidence: 2b). Limitations of that study were discussed. Evidence from the studies by Tokuda *et al.*[3] and Motzer *et al.*[13] involved subgroups within a retrospective series that included a cumulative total of 49 patients (level of evidence: 4). Although the quality of this immunotherapy evidence was quite poor, conclusions can be reached from the homogeneity of both studies in demonstrating no effect of immunotherapy. Trying an approach that has worked for other rare diseases, such as a disease registry, may be warranted[41].

### 5. CONCLUSIONS

Collecting duct carcinoma is a rare subtype of RCC. It is aggressive, presents symptomatically at an advanced stage, and has a poor prognosis. A systematic review of the literature on management options for CDC reveals that the only studied treatment is a GC regimen for which a 26% (95% CI: 8%–44%) partial or complete response rate in 23 patients was observed. The role of targeted therapy (tyrosine kinase inhibitors such as sunitinib or sorafenib) in the management of CDC has not been established based on limited data to date.

### 6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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