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*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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*CASE REPORT*

# Conversion therapy in advanced perihilar cholangiocarcinoma based on patient-derived organoids: A case report

Yong-Gang He, Ling-Yu Zhang, Jing Li, Zheng Wang, Chong-Yu Zhao, Lu Zheng, Xiao-Bing Huang

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## Abstract

### *BACKGROUND*

Patient-derived organoids (PDOs) have been demonstrated to predict the response to drugs in multiple cancer types. However, it remains unclear about its application in cholangiocarcinoma.

### *CASE SUMMARY*

A 59-year-old woman was admitted to the hospital due to upper abdominal pain for over 8 months. According to relevant examinations, she was diagnosed as perihilar cholangiocarcinoma (pCCA) with intrahepatic metastasis and perihilar lymphatic metastasis. After multidisciplinary team discussion, percutaneous transhepatic cholangiodrainage was performed to relieve biliary obstruction, and puncture biopsy was conducted to confirm the pathological diagnosis. Transarterial chemoembolization with nab-paclitaxel was used in combination with toripalimab and lenvatinib, but the levels of tumor markers including alpha fetal protein, carcinoembryonic antigen, carbohydrate antigen 15-3 and cancer antigen 125 were still raised. The PDO for drug screening showed sensitive to gemcitabine and cisplatin. Accordingly, the chemotherapy regimen was adjusted to gemcitabine and cisplatin in combination with toripalimab and lenvatinib. After 4 cycles of treatment, the tumor was assessed resectable, and radical surgical resection was performed successfully. One year after surgery, the patient was still alive, and no

recurrence or occurred.

*CONCLUSION*
PDOs for drug sensitivity contribute to screening effective chemotherapy drugs for advanced pCCA, promoting conversion therapy and improving the prognosis.

**Key Words:** Patient-derived organoids; Perihilar cholangiocarcinoma; Conversion therapy; Drug screening; Intrahepatic metastasis; Case report

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**Core Tip:** The patient-derived organoids (PDOs) have been demonstrated to predict the response to drugs in multiple cancer types. Here we first descried a patient with advanced perihilar cholangiocarcinoma (pCCA) who successfully underwent surgical resection after use of the PDO-guided gemcitabine and cisplatin in combination with toripalimab and lenvatinib and achieved good prognosis. For advanced pCCA patients, the PDO-based drug sensitivity testing contributes to screening effective chemotherapy drugs to promote the personalized treatment, which not only creates opportunities for surgical resection by lessening the tumor, but also offers a novel platform for improving the patient's prognosis.

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## INTRODUCTION

Cholangiocarcinoma (CCA) is a heterogeneous group of malignancies arising from the epithelium of the bile ducts, with pathological characteristics of biliary tract differentiation[1]. Anatomically, CCA can be classified as intrahepatic, perihilar, and distal subtypes, among which perihilar CCA (pCCA) was most common, approximately accounting for 50%[2]. Due to aggressiveness, late diagnosis, and refractory nature, the mortality of CCA is high[3]. It is reported that the tumor can be resected completely in only about a third of cases, for other unresectable cases systemic chemotherapy with gemcitabine and cisplatin is considered as the first-line treatment option, but the prognosis remains dismal[4]. Therefore, it is indispensable for developing the optimal therapeutic strategies to further understand the CCA biology, oncogenic landscape, and its complex interaction with tumor microenvironment.

Although two dimensional cultures for CCA cell lines and xenograft animal models are the standard experimental models in CCA studies, they fail to recapitulate the key characteristics of an *in-vivo* growing tumor. Organoids, an *in-vivo* three dimensional (3D) culture technology, have been demonstrated to recapitulate both the pathology of the cells in patient-derived tissues and the native physiology of the cells in healthy tissues of origin[5], and can be generated from liver biopsies of patients with primary liver cancers including CCA, with the capability of highly retaining the histological features and genetic alterations from parental tumor tissues[6]. In a previous study, the drug response differed among individuals after the patient-derived organoids (PDOs) were treated with sorafenib, indicating the potential of PDOs in guiding individualized chemotherapy regimens[7]. Here, we describe a patient with advanced pCCA who successfully underwent surgical resection after treatment with PDO-guided gemcitabine and cisplatin in combination with toripalimab and lenvatinib.

## CASE PRESENTATION

### *Chief complaints*
A 59-year-old woman was admitted to the hospital because of upper abdominal pain for over 8 months.

### *History of present illness*
Upper abdominal pain lasted for more than 8 months.

### *History of past illness*
The patient previously underwent tubal ligation, and had chronic hepatitis B.

### *Personal and family history*
The patient denied any family history of malignant tumors.

### *Laboratory examinations*

Laboratory examinations showed alanine aminotransferase of 374.3 IU/L, aspartate aminotransferase of 264.3 IU/L, total bilirubin of 65.2 μmol/L, direct bilirubin of 41.4 μmol/L, alpha fetal protein (AFP) of 2.23 ng/mL, carcinoembryonic antigen (CEA) of 16.68 ng/mL, carbohydrate antigen (CA) 15-3 of 112 U/mL, CA19-9 of 136.13 U/mL and CA125 of 1 000 U/mL (Table 1).

### *Imaging examinations*

Computed tomography (CT) showed a space-occupying lesion in the hepatic hilar region and multiple hemangiomas in the liver, with the possibility of metastatic tumors in the liver S2 and S8 segments (Figure 1A-C). Magnetic resonance imaging (MRI) revealed space-occupying lesions in the liver S2 and S8 segments, various swollen lymph nodes in the hepatic hilar region, as well as multiple hemangiomas in the liver S4-6 segments. In combination with positron emission tomography-CT, pCCA with intrahepatic metastasis and perihilar lymphadenectasis was diagnosed.

## FINAL DIAGNOSIS

In combination with relevant examinations, the patient was finally diagnosed with pCCA with intrahepatic metastasis and perihilar lymphatic metastasis.

## TREATMENT

After multidisciplinary team discussion, percutaneous transhepatic cholangiodrainage was performed to relieve biliary obstruction, and needle biopsy was conducted to confirm the pathological diagnosis. Meanwhile, the organoids from biopsy samples were cultured after the informed consent form was obtained from the patient. Briefly, the tumor tissues obtained were washed with precooled phosphate buffer saline and then minced. After 30-minute digestion, cell pellets were collected *via* centrifugation. Pipettes were used to seed the cells and Matrigel suspension onto 6-well plates (2 mL *per* well) following addition of Matrigel, and the plates were placed in a 37 °C incubator for 15 min. When the droplets were fully solidified, the culture medium (Kingbio Medical Co., Ltd., Chongqing, China) was added. Subsequently, the plates were placed into an incubator (37 °C, 5% carbon dioxide) for culture. The culture medium was replaced every 2-3 days, and drug sensitivity testing was performed until organoids grew like solid spheroids with a diameter of about 70 μm (Figure 2A).

According to the patient's condition, transarterial chemoembolization with nab-paclitaxel (125 mg/m$^2$) was used in combination with toripalimab (240 mg, once every 3 weeks) and lenvatinib (40 mg *per* day). Two weeks later, the levels of all tumor markers above went up by varying degrees except for slightly decreased CA19-9 (Table 1). The organoid drug sensitivity testing showed sensitive to gemcitabine and cisplatin (Figure 2B). Based on this, the chemotherapy regimen was adjusted to gemcitabine (1000 mg/m$^2$) combined with cisplatin (25 mg/m$^2$), but the use of toripalimab and lenvatinib remained unchanged. After 4 cycles of treatment, the levels of AFP, CEA, CA15-3, CA19-9 and CA125 all returned to the normal range (Table 1). CT and MRI both indicated significantly lessened liver tumor diameter (Figure 1D-F). The tumor was assessed as resectable according to response evaluation criteria in solid tumors (version 1.1). Postoperative pathological results showed moderately differentiated tubular adenocarcinoma with visible vascular cancer emboli and partial hepatic steatosis in the liver tumor, but without perineural invasion and residual cancer tissues. Additionally, a cavernous hemangioma in the liver (S4B + S5 segments) and chronic cholecystitis were observed, but with no tumor cells in the incisal edge.

## OUTCOME AND FOLLOW-UP

At 12 months postoperatively, the patient was still alive, and the CT scan showed no recurrence or metastasis (Figure 1G-I).

## DISCUSSION

As the most common type of CCA, pCCA originates from the extrahepatic biliary tree proximal to the origin of the cystic duct and is borne by a complex diagnostic iter[8]. Although great development has been achieved in surgical strategies over the past decades, the postoperative 5-year survival rate remains to be low, often close to 20%[9]. Surgery is the preferred treatment method, but most patients with pCCA are unresectable at the time of diagnosis. In recent years, use of aggressive approaches based on various imaging modalities and specific perioperative management has been confirmed to improve the prognosis of pCCA patients by converting the palliative therapies to the radical surgery[10,11]. In this study, under the guidance of the pCCA organoid for drug screening, the patient successfully received surgical resection after use of gemcitabine and cisplatin in combination with toripalimab and lenvatinib, and no recurrence and metastasis occurred 1 year after surgery.

**Table 1 Changes of tumor markers at different time points during treatment**

| Indicators | AFP (ng/mL) | CA19-9 (U/mL) | CEA (ng/mL) | CA125 (U/mL) | CA15-3 (U/mL) |
|---|---|---|---|---|---|
| On admission | 2.23 | 136.13 | 16.68 | 1000 | 112 |
| After treatment for 2 weeks | 5.86 | 127.24 | 20.25 | 1210 | 122 |
| After organoid-based treatment for 4 cycles | 2.12 | 43.84 | 4.21 | 16 | 12.2 |
| First year after surgery | 2.3 | 39.67 | 2.62 | 21.2 | 10.6 |

AFP: Alpha fetal protein; CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen.

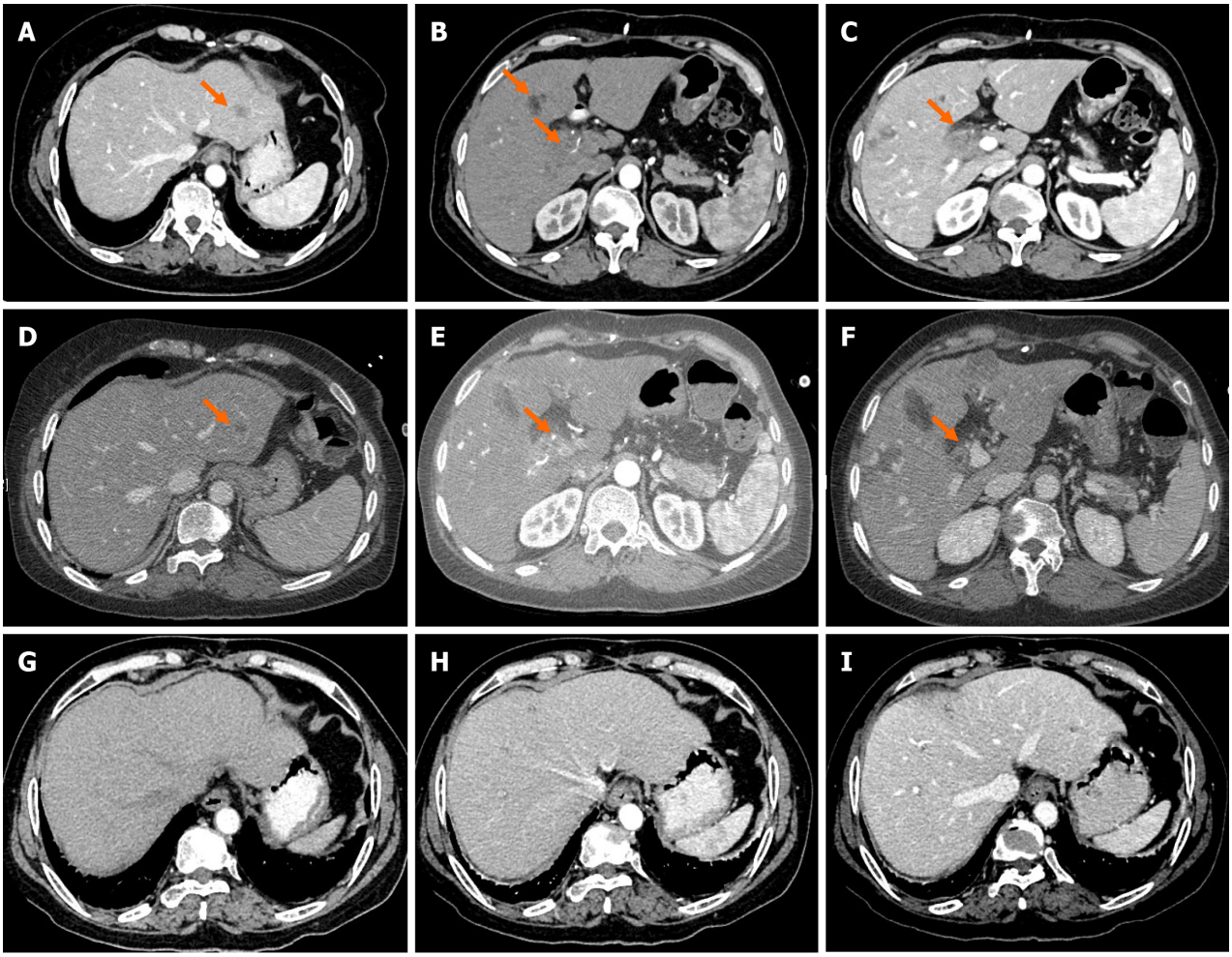


**Figure 1 Computed tomography images.** A-C: Computed tomography (CT) images of the patient on admission; D-F: CT images of the patient before surgery; G-I: CT images of the patient 1 year after surgery. The orange arrows head towards the tumor.

Except for surgical resection, pre- and post-operative multidisciplinary treatment for CCA plays a crucial role in survival improvement. Neoadjuvant therapies involving chemotherapy and transarterial embolization have been demonstrated to downgrade the unresectable intrahepatic CCA, thus allowing for the implementation of radical surgical resection[12,13]. For patients with advanced CCA, the purpose of neoadjuvant therapy is to convert the unresectable tumors into the resectable ones to ameliorate the long-term prognosis. McMasters *et al*[14] found that preoperative chemoradiation for extrahepatic CCA contributed to producing significant antitumor responses, which might improve the capability of obtaining the tumor-free resection margin. When the neoadjuvant therapy with gemcitabine and S-1 chemotherapy was used for pCCA, the 5-year disease-specific survival was 50.3% in the resected and 30.0% in the borderline resected but only 16.5% in the locally advanced patients[15]. Moreover, in an open-label, single-arm, phase 2 study, gemcitabine/S-1 neoadjuvant therapy was identified to effective and tolerable in patients with borderline resectable pCCA, respectively with the median survival time of 50.1 months for the resected and 14.8 months for the unresected[16]. To date, however, the evidence of neoadjuvant therapy for CCA, especially pCCA, has not been built completely.

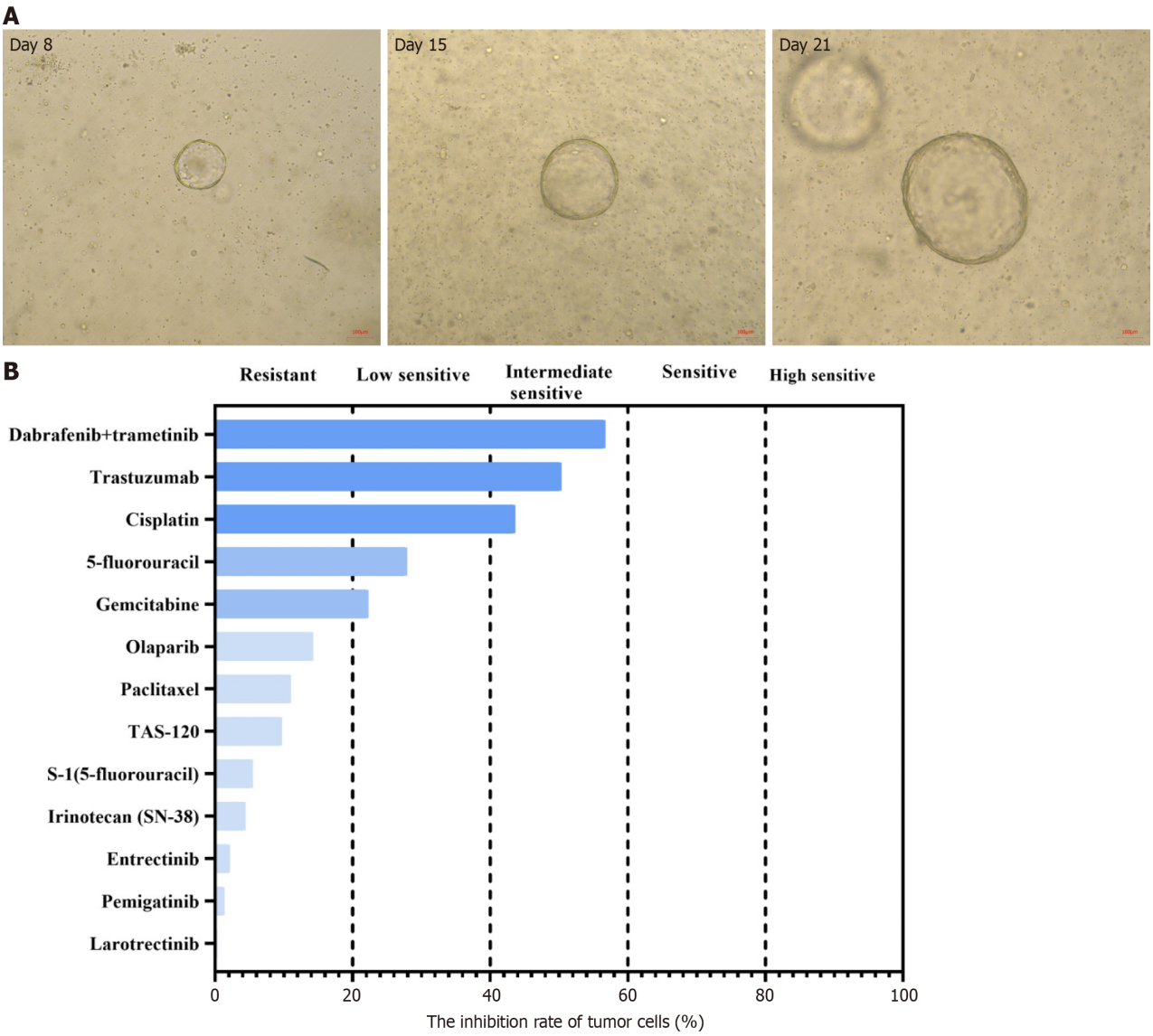


**Figure 2 The status of organoid formation at different time points of perihilar cholangiocarcinoma.** A: Using an optical microscope; B: The organoid-based drug sensitivity results.

With the emergence of more novel and effective chemotherapy, targeted therapy, and immunotherapy, multi-drug combination therapy is proposed to treat advanced CCA. Although gemcitabine combined with cisplatin is considered as the first-line treatment for advanced CCA, the median overall survival was still less than 1 year[17], and no standard treatment is recommended beyond the first-line chemotherapy. In this study, in addition to gemcitabine and cisplatin, toripalimab and lenvatinib were also used as the neoadjuvant therapy, and the tumor was converted into the resectable, suggesting that gemcitabine and cisplatin in combination with toripalimab and lenvatinib may be a promising conversion therapy strategy for patients with advanced pCCA. Importantly, this patient did not experience any recurrence and metastasis 1 year following treatment.

The PDO, a novel 3D preclinical model, has the capability of highly preserving the histopathological, genetic, and molecular characteristics of the original tumor, which can simulate *in vivo* and *ex vivo* responses observed in patients and open the new way for guiding therapeutic decisions[18]. It can be established in a clinically meaningful time of 6-10 weeks, with the positive predictive value of 88% and negative predictive value of 100% in predicting the patient's response[19]. Importantly, the neoadjuvant treatment response could also be predicted by the PDOs[20]. By comparing responses to antitumor agents in PDOs and PDO-based xenograft models with those of patients in clinical trials, Vlachogiannis *et al*[19] found that PDOs could recapitulate the patients' clinical response and could be conducted in precision medicine protocols. Based on pharmaco-typing, PDOs was confirmed to be a predictive biomarker for clinical treatment responses to standard-of-care chemotherapeutics[21].

Recently, several studies on the clinical application of PDOs in CCA have all shown that CCA PDOs contribute to identification of effective cancer drugs to guide the individualized treatment, highlighting the importance of PDOs as *in vitro* models of CCA [6,7,22]. It was reported that the generation success rates of organoids from hepatocellular carcinoma and intrahepatic CCA needle biopsies were 33% and 60%, respectively[7], lower than 75%-83% in pancreatic cancer[23] and 90% in colorectal cancer[24], which might be associated with absence of epithelial stem cell features in hepatocytes. In

this study, we successfully established the pCCA organoids from needle biopsy samples and found that chemotherapeutic drugs gemcitabine and cisplatin were potential candidates for the patient. Accordingly, the neoadjuvant chemotherapy with gemcitabine and cisplatin was used in combination with toripalimab and lenvatinib. The tumor was assessed resectable after treatment, and radical surgical resection was performed successfully. Our findings suggest that the drug sensitivity testing based on pCCA organoids helps screen the appropriate chemotherapy drugs for advanced pCCA patients, consequently promoting conversion therapy and improving the prognosis. Jensen *et al*[25] performed a prospective clinical study based on the PDOs to treat metastatic colorectal cancer after standard treatments, and demonstrated improved clinical outcomes compared with those expected from the best supportive care alone, suggesting that cancer patients may derive benefits from the PDO functional testing. Importantly, the treatment methods based on tumor organoids play a key role in guiding conversion therapy for intrahepatic CCA[26]. Thus, the PDOs may be a promising technology for conversion therapy to improve the prognosis at the patient-specific level.

## CONCLUSION

For advanced pCCA patients, the PDO-based drug sensitivity testing contributes to screening effective chemotherapy drugs to promote the personalized treatment, which not only creates opportunities for surgical resection by lessening the tumor, but also offers a novel platform for improving the patient's prognosis.

## FOOTNOTES

**Author contributions:** He YG and Zhang LY were responsible for writing the manuscript; Li J, Wang Z, and Zhao CY were responsible for data acquisition and investigation; Zheng L and Huang XB reviewed the manuscript; All authors contributed to the study and approved the submitted version.

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