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# Case report: Conversion therapy for advanced intrahepatic cholangiocarcinoma using PD-1 inhibitor plus S-1 and nab-paclitaxel

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Intrahepatic cholangiocarcinoma (iCCA) is a highly malignant hepatobiliary tumor with a high rate of advanced disease at initial presentation. Conversion into resectable iCCA is important for improving the prognosis. Immunotherapy-based regimens are being increasingly used for treating advanced iCCA in recent years. However, the use of combined chemotherapy and immunotherapy for conversion has rarely been reported. The aim of this report was to present the outcomes of a 52-year-old female patient with IIIB iCCA. The patient was treated with a programmed cell death protein-1 inhibitor plus S-1 and nab-paclitaxel. The postoperative histopathological results indicated pathologic complete response after six cycles of systematic treatment. The patient is currently disease-free for one year.

## KEYWORDS

intrahepatic cholangiocarcinoma, case report, conversion therapy, complete remission, immunotherapy combined therapy

## Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common liver malignancy after hepatocellular carcinoma (1); it is a highly malignant hepatobiliary tumor with an increasing incidence (2). Most of cases of iCCA are diagnosed in advanced stages at presentation, with a median survival of less than one

year. Most patients are therefore no longer eligible for radical surgery, and chemotherapy forms an important part of treatment.

First-line chemotherapy for advanced iCCA includes gemcitabine, a platinum derivative, nab-paclitaxel, and fluoropyrimidines (3). However, only a few chemotherapy studies on chemotherapy were designed for iCCA alone. The BILCAP study compared capecitabine with observation following resection in patients with biliary tract cancer patients following resection. The median overall survival was prolonged from 36 months to 53 months in the capecitabine group (4). The ABC-06 study randomly compared folinic acid, fluorouracil, and oxaliplatin chemotherapy (FOLFOX) plus active symptom control with active symptom control alone as a second-line treatment for biliary tract cancer patients following cisplatin and gemcitabine failure (5). The results indicated that the FOLFOX regimen improved the overall survival rate by 14.5% at 12 months. In recent years, programmed cell death protein-1 (PD-1) inhibitors have shown effectiveness in conversion therapy for advanced liver cancer (6–9). An increasing number of studies are reporting promising outcomes with immunotherapy plus chemotherapy or targeted therapy for advanced liver cancer (10–17). Research indicates that iCCA has a rich tumor stroma; this suggests that immunotherapy may offer benefits in this tumor (18, 19). However, the outcomes with immunotherapy have been found to be unsatisfactory (19). Different studies indicate that chemotherapy, and especially 5-FU analogues, could upregulate programmed cell death ligand-1 (PD-L1) expression in tumor tissue and enhance the therapeutic effect of immunotherapy (20–26). However, the clinical benefit of immunotherapy plus chemotherapy for advanced iCCA remains unclear.

This report presents the results of a new combined regimen with chemotherapy and immunotherapy for advanced iCCA, that offered successful conversion for radical resection. The postoperative specimen showed pathological complete response according to the Response Evaluation Criteria in Solid Tumors (version 1.1). The episode of care for this patient is summarized in Figure 1A.

## Case description

A 52-year-old woman was admitted to our hospital with jaundice for 6 days. She did not have a history of chronic hepatitis B or C infection. The Eastern Cooperative Oncology Group performance status score was 0. The total and direct bilirubin levels were 232.7  $\mu\text{mol/L}$  and 186.1  $\mu\text{mol/L}$ , respectively, the alpha-fetoprotein level exceeded 1000 ng/ml, and the cancer antigen 19-9 level was 96.06 units/ml; the carcinoembryonic antigen level was within normal limits. An upper abdominal enhanced computed tomography (CT) scan showed a tumor measuring 5.8 cm in longest diameter in segment 4 of the liver. The portal vein phase indicated that the tumor had invaded the middle hepatic vein

and the umbilical portion of the left portal vein and was adjacent to the main trunk of the right portal vein (Figures 1B–D). The tumor had also invaded the liver hilum, leading to biliary obstruction.

## Diagnostic assessment, therapeutic intervention, follow-up, and outcomes

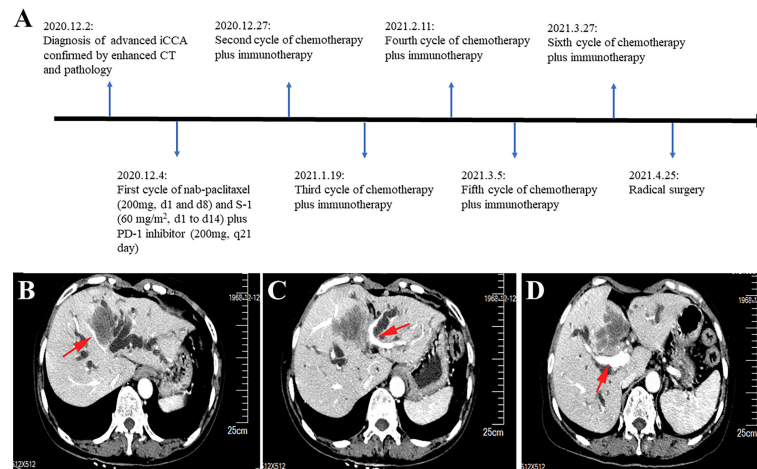
The patient underwent CT-guided percutaneous liver core biopsy and percutaneous transhepatic cholangiodrainage. Cytology confirmed the presence of cancer cells (Figure 2A); the results of immunohistochemical analysis were as follows: CK7 (+), CK19 (+), AFP (-), Hepatocyte (-), VILLIN (+), MOC-31 (+), GATA-3(-), CD34 (-), Glypican-3 (-), and Ki-67 labelling index: 70% (Figure 2B). According to the American Joint Committee on Cancer staging system, 8th edition, the patient was diagnosed with stage IIIB (T2N1M0) iCCA.

According to the opinion of a multidisciplinary team, she then received chemotherapy and immunotherapy after the total bilirubin had returned to the normal level following percutaneous transhepatic cholangiodrainage. After six cycles of treatment with nab-paclitaxel (200 mg, d1 and d8), S-1 (60 mg/m<sup>2</sup>, d1 to d14), and a PD-1 inhibitor (200 mg, q21 days), an enhanced CT scan showed that the longest diameter of the tumor shrank from 5.8 cm to 3.8 cm (Figures 3A–C). The treatment response was evaluated to be a partial response according to the revised Response Evaluation Criteria in Solid Tumors (version 1.1). The patient developed myelosuppression during the third cycle of chemotherapy and recovered on administration of growth factor injections. No immune-related adverse events were observed.

After surgical reassessment, the patient underwent hepatectomy (H2345'8'-B-MHV) (27), cholecystectomy, and biliodigestive anastomosis. Biliary leakage occurred on postoperative day seven and recovered after one month. No viable tumor cell was detected in the resected specimen; only necrotic tissue was detected, indicating a pathologic complete response after systematic treatment (Figure 2C). Additionally, the tissue in lymph node stations 7, 8, 9, and 12 were found to be entirely necrotic. The postoperative pathology results indicated down staging of the tumor to stage T1aN0M0 without perineural and vessel invasion; the resection margins indicated R0 resection status.

## Follow-up and outcome

The patient was discharged on postoperative day 31 and monitored every 3 months for recurrence at a local hospital by CT or magnetic resonance imaging. During the recent telephonic follow-up in May 2022, the patient informed that she was living a normal daily life without any symptoms. She had



**FIGURE 1**  
 Timeline and enhanced computed tomography scan at the time of diagnosis. **(A)** Showing the course of initial diagnosis, medication, and surgery. **(B)** Showing a large mass in segment 4 of the liver invading the middle hepatic vein. **(C)** Showing the mass in segment 4 of the liver invading the umbilical portion of the left portal vein. **(D)** Showing the mass adjacent to the main trunk of the right portal vein.

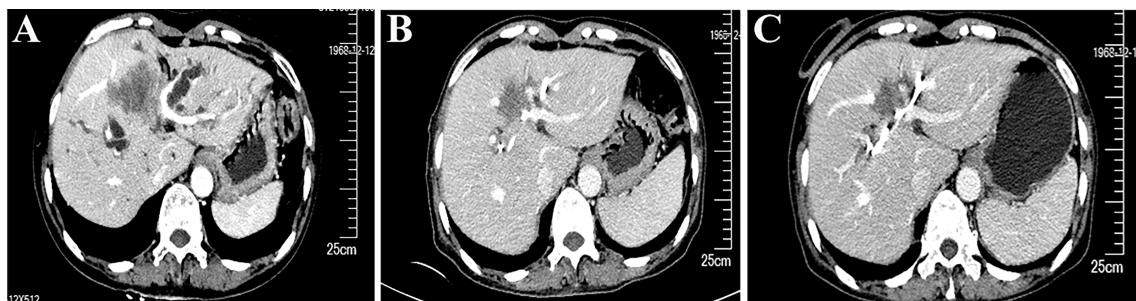
therefore achieved disease-free for one year and will undergo periodic radiographic follow-up.

## Discussion

To date, iCCA remains a challenging tumor without an effective treatment. Due to the highly aggressive nature of the cancer and its insidious onset, approximately 65% of cases are diagnosed in advanced stages with a median survival of less than 1 year. However, the median disease-free survival can rise up to three years after resection. Therefore, radical surgery after systemic treatment for unresectable iCCA has recently received increasing attention. The case in our study shows that conversion therapy for advanced iCCA can be achieved using a PD-1 inhibitor plus S-1 and nab-paclitaxel; this triplet regimen is safe and effective.

The patient initially presented with jaundice due to tumor compression. Preoperative biliary decompression has been traditionally performed in patients having malignant biliary obstruction with resectable tumors (28). However, growing evidence indicates that preoperative biliary decompression could increase postoperative complications (29–32). In patients with unresectable tumors, biliary decompression is necessary for improving liver function and facilitating subsequent chemotherapy. Complications associated with biliary decompression were not observed in our case.

The patient was evaluated *via* enhanced CT scans before treatment and was found to have N1 lymph node status. Lymph node dissection (LND) is recommended by the American Joint Committee on Cancer staging system, 8th edition, which suggests that at least six lymph nodes should be removed during LND (2). In this context, Kim et al. recommended that at least lymph node



**FIGURE 2**  
 Cytologic examination and hematoxylin-eosin (HE) staining of liver tumor tissue from the needle biopsy and resected specimen. **(A)** Cytologic examination shows the presence of cancer cells (1000 $\times$ ). **(B)** HE staining (200 $\times$ ) of the liver tumor tissue from the needle biopsy. **(C)** HE staining (100 $\times$ ) shows only necrotic tissue in the resected tissue.

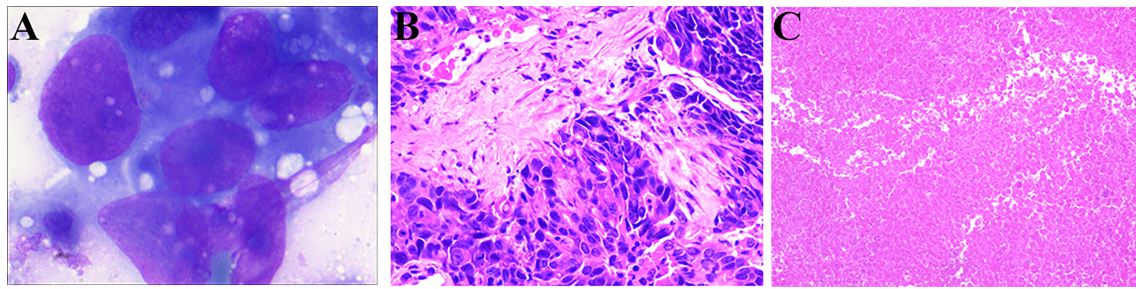


FIGURE 3

Enhanced computed tomography (CT) scans show that the cancer lesion changed over time. (A) CT results (2020.12.2) at the time of diagnosis. (B) CT results (2020.2.9) before the fourth cycle of treatment. (C) CT results (2020.4.23) before the radical surgery.

stations 8 and 12 should be dissected irrespective of the tumor location. Although LND is effective for evaluation of nodal status, studies are becoming increasingly skeptical about the benefits of LND for prognostication (33–35). To date, routine LND remains controversial; however, a multi-center study shows that selected patients with iCCA could benefit from LND (36).

Numerous studies on hepatocellular carcinoma have indicated that systemic conversion chemotherapy could make unresectable cases resectable (6, 7). However, conversion therapy for iCCA is relatively understudied. In a phase 2 clinical trial, nine of 41 (22%) patients with unresectable iCCA were successfully converted to surgically operable status using selective internal radiotherapy combined with chemotherapy (cisplatin and gemcitabine) (37). Riby et al. reported that 32 cases with initially unresectable iCCA in their cohort were resectable after administration of down staging chemotherapy with or without selective internal radiotherapy (38). In 2020, a French study tested FOLFIRINOX as first-line chemotherapy for advanced iCCA; 1 secondary resection was performed among 21 patients (39). In these studies, multiple chemotherapeutic agents were used to achieve good down staging. However, a combined chemotherapy regimen may be associated with severe adverse events. In another phase 2 trial, 60 patients with advanced biliary tract cancers were administered a regimen of nab-paclitaxel plus gemcitabine and cisplatin; nine (16%) patients withdrew owing to adverse events (40).

Although immunotherapy has demonstrated remarkable potency for different cancers, its efficacy in iCCA remains to be tested (41, 42). The KEYNOTE-158 study recruited 22 patients with cholangiocarcinoma who received immunotherapy; the overall response rate was 40.9% with a median progression free survival of 4.2 months (43). A phase II trial enrolled 54 patients with biliary tract cancer, including 32 cases of iCCA; the patients received at least one dose of immunotherapy and obtained a median progression free survival of 3.7 months (44).

Several ongoing studies are evaluating the efficacy of immunotherapy combined with gemcitabine with or

without cisplatin; their results will be of particularly clinical value (18). In this case, we adopted a different combination of immunotherapy (PD-1 inhibitor) with S-1 plus nab-paclitaxel. S-1 is a prodrug of the active substance fluorouracil (5-FU); it can be preferentially converted to 5-FU in tumor cells (45). Studies indicate that 5-FU could induce PD-L1 expression in different cancers, including colorectal, gastric, and pancreatic cancer (20–26). Thus, we assumed that 5-FU may also upregulate PD-L1 expression in the tumor microenvironment of iCCA. The final pathological results support our hypothesis, as no active tumor cells were found in the specimen. A recent study reported a similar outcome to that of ours; in that study, a patient with advanced iCCA survived for over 16 months without progression after being treated with a PD-1 inhibitor plus capecitabine (46). Another group also successfully converted advanced iCCA to resectable status with PD-1 and tyrosine kinase inhibitors (47). These results indicate that immunotherapy may have a broader prospect in the conversion of advanced iCCA.

Although our results are promising, there are some limitations to this report. First, this report describes only one successful case; whether other patients are sensitive to this combined regimen is still unknown. A clinical trial with more patients will be needed to confirm our findings. Second, we could not test the expression level of PD-L1 due to complete necrosis of the tumor in the postoperative specimen. Further larger studies are needed to confirm whether 5-FU analogues may upregulate PD-L1 in iCCA.

## Conclusion

The findings from our case suggest that our regimen (S-1 and nab-paclitaxel plus PD-1 inhibitor) is suitable for converting advanced iCCA to resectable status; this provides a new treatment choice for this tumor. However, as this report describes only one case, studies on more patients are needed to verify its effectiveness in future.

## Patient perspective

When I got jaundice, I knew that something terrible happened to me. I was admitted to our local hospital and ordered a series of tests. After the results came out, the doctor asked me to transfer to the territorial central hospital. After I came to the territorial central hospital, the doctors kept encouraging me. While my jaundice improved, the doctor ordered chemotherapy and immunotherapy. At each post-treatment review, the doctor told me that the tumor was shrinking. It gave me great confidence in my treatment and made me forget the pain of chemotherapy. Finally, the doctor said to me that I was eligible for surgery. I felt a hope of rebirth. The operation was successful, and I am very grateful to the doctors. Until now, no tumor recurrence was found on postoperative monitoring. I am delighted with the treatment effect and feel confident for the future.

## Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**. Further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of Xiangyang Central Hospital. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

XCL, XGL, XFL, YJW, and WG conceived the idea for the article. XCL and ZYJ drafted the manuscript. XGL approved the

final version of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.935817/full#supplementary-material>

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