doi.org/10.36721/PJPS.2025.38.4.REG.13496.1

Effects of radical surgery, chemotherapy combined with PD-1 inhibitor camrelizumab on prognosis of hilar cholangiocarcinoma patients and its clinical significance

Yuchen Liu[1,2], Jianjiao Zhu[1,2], Fanning Xie[1,2], Jilin Tao[1,2] and Jingdong Li[1,2]*

[1]Department of Hepatobiliary Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China
[2]Institute of Hepato-Biliary-Pancreatic-Intestinal Disease, North Sichuan Medical College, Nanchong, China

Abstract: Hilar cholangiocarcinoma (HCCA), a malignant bile duct tumor, has an obscure pathogenesis. We aimed to assess the therapeutic effects of surgery and chemotherapy combined with the PD-1 inhibitor camrelizumab on HCCA patients' prognosis. This study included 26 HCCA patients. Post-surgery, patients received camrelizumab (3mg/kg IV) every 3 weeks, oxaliplatin (100 mg/m2) weekly and gemcitabine (1000 mg/m2) biweekly. Computed tomography assessed treatment response after 6 weeks and survival was evaluated through quarterly follow-ups. Among the 26 patients, 2 achieved complete response, 9 partial response, and 5 stable disease, while 10 progressed. The objective response rate (ORR) and disease control rate (DCR) were 42.3% and 61.5%, respectively. Successful down staging was observed in 16 patients. Post-treatment, AST and ALT levels significantly increased. The overall survival (OS) and disease-free survival (DFS) rates were 76.9% and 69.2%, respectively. Sensitive patients (with down staging) had significantly better survival than non-sensitive patients. Radical surgery and chemotherapy combined with camrelizumab may be effective and safe for HCCA management. Statistical analyses were performed using GraphPad Prism version 7.0, employing Student's t-tests for comparisons between groups.

Keywords: HCCA, radical surgery, chemotherapy, camrelizumab, hilar cholangiocarcinoma

Submitted on 27-09-2024 – Revised on 07-11-2024 – Accepted on 06-01-2025

INTRODUCTION

Hilar cholangiocarcinoma (HCCA) is a malignant tumor derived from bile duct mucosa epithelium, accounting for approximately 60% of cholangiocarcinoma cases (Soares and Jarnagin, 2021). The median age of patients diagnosed with HCCA is around 50 years, with the incidence risk being notably low for individuals under 40 years old, at about 5%, and peaking for patients around 70 years old, at nearly 30% (Sapisochin *et al*., 2020; Elvevi *et al*., 2022). Risk factors for HCCA include bile duct stones (intrahepatic and extrahepatic), viral hepatitis (types B and C), obesity, congenital liver fibrosis, Caroli's disease, bile duct cysts, primary sclerosing cholangitis (PSC), liver fluke disease and acute suppurative cholangitis. Additionally, pancreatic enzyme reflux, bile stasis, chronic inflammation, apoptosis, aging and cell renewal are believed to be correlated with the development of HCCA (Anderson and Doyle, 2019; Zhang *et al*., 2021). Despite ongoing investigations, the pathogenesis of hilar cholangiocarcinoma remains elusive.

Currently, surgical radical resection is the sole curative approach for HCCA, with a cure rate of only about 20% (Zhang *et al*., 2022). The unique tumor location and growth pattern of HCCA often lead to obstructive jaundice and cholestatic hepatitis, resulting in increased postoperative complications. Furthermore, HCCA patients typically exhibit poor therapeutic responses to alternative treatments such as radiotherapy and chemotherapy, with survival rates disappointingly ranging from 20% to 40% (Lee *et al*., 2022; Xia *et al*., 2022).

With advancing knowledge of HCCA pathogenesis, targeted therapy has seen rapid development, focusing on key carcinogenic targets at the cellular and molecular levels, including antigens, receptors, or gene fragments (Zhao *et al*., 2021; Quinn *et al*., 2023). These therapies are designed to reach tumors through fluid circulation, bind specifically to carcinogenic sites, and induce tumor cell necrosis, apoptosis, or immune cell engulfment, without affecting surrounding normal tissue cells. Several drugs targeting main signaling pathways of cholangiocarcinoma, such as epidermal growth factor receptor inhibitors (Cetuximab, Erlotinib, Gefitinib), vascular endothelial growth factor inhibitors (Sorafenib, Bevacizumab), Her-2 inhibitors (Trastuzumab, Lapatinib), and Raf kinase inhibitors (Sorafenib), have been approved for clinical trials. Preliminary clinical trial results suggest a potential positive effect of Cetuximab combined with chemotherapy on HCCA treatment, though further research is imperative (Zhao *et al*., 2021, Forde PM, *et al*., 2018). Therefore, in addition to radical surgery, the combination of targeted drugs with conventional chemotherapy may improve the survival rate and overall prognosis for HCCA patients.

Our study, conducted at North Sichuan Medical College, enrolled 26 patients who met the admission criteria and

**Corresponding author:* e-mail: yasionlau@163.com

were admitted between July 2019 and November 2022. We analyzed the therapeutic effects of surgery and chemotherapy combined with the PD-1 inhibitor camrelizumab on HCCA patients and their prognosis. We aim to contribute a novel approach to the clinical management of HCCA.

MATERIALS AND METHODS

Patients

Between July 2019 and November 2022, 26 HCCA patients undergoing HCCA surgery and immune checkpoint inhibitor camrelizumab have been including as the study subject in the current retrospective work. The inclusion criteria were: (1) Patients between 40-70 years old; (2) Diagnosed as HCCA through B-ultrasound, abdominal CT, MRI, and other examinations, patients can successfully be conducted with standardized R0 radical surgery+ regional lymph node dissection; (3) The liver function of candidates with child-pugh score A or B (see table 1 for the child-pugh score); (4) Patients without other serious systemic diseases (5) Physical condition score (see table 2 for ECOG score of physical condition): ECOG score 0 or 1. Exclusion criteria: (1) Does not meet the inclusion criteria; (2) Individuals with severe coagulation disorders; (3) Merge with other tumors; (4) Those who are unwilling to participate. Exclusion criteria: (1) Candidates have severe postoperative complications or have severe adverse chemotherapy events; (2) Patients who do not have a response to camrelizumab after gene sequencing. (3) Patients who lost contact and were unable to follow up. The current work has been approved by the ethic committee of North Sichuan Medical College, every patient agree to participate in current work, therefore signed the informed consent documents. Ethical approval number: 202210621.

Treatment methods

The resection has been conducted based on the standard surgical guidelines. After surgery, the patients received camrelizumab (intravenous administration) with a dosage of 3mg/kg every 3 weeks; besides, the patients received 100 mg/m2 oxaliplatin every week and 1000 mg/m2 gemcitabine every 2 weeks.

Treatment outcomes

Computed tomography was conducted after treatment for 6 weeks for evaluating the response of the patients to the therapies. Moreover, the patients have been followed up every 3 months for overall survival (OS) as well as disease-free survival (DFS).

Liver function test

Liver function tests before and after treatment have been conducted by the clinical laboratory department of North Sichuan Medical College. The AST and ALT of the patients were compared.

Table 1: Baseline information of the patients.

Gender	
Male	15
Female	11
Age (years), median (range)	
<60	10
≥60	16
Gallstone	
Yes	8
No	18
Diabetes	
Yes	3
No	23
Hypertension	
Yes	3
No	23
ECOG score	
0-1	25
2-5	1
Tumor size	
<3	2
3-5	8
≥5	16
T stage	
T1	9
T2	5
T3	4
T4	8
N stage	
N0	14
N1	12
M stage	
M0	21
M1	5
TNM stage	
I	8
II	8
IIIA	5
IIIB	0
IV	5

STATISTICAL ANALYSIS

GraphPad (version 7.0, San Diego, CA, USA) has been applied to evaluate the data. Data have been displayed as mean ± standard deviation (SD). Comparison has been conducted by student-*t* test. Kaplan–Meier methods have been used to evaluate the survival. $P<0.05$ has been considered a significant difference.

RESULTS

Baseline information of the patients

Information on all candidates is presented in table 1. Of the 26 enrolled patients with HCCA, 15 were males and 11 were females. There are 10(38.5) patients under sixty years, while 16(61.5%) are >60 years, patients' average

age was 60.42; meanwhile, 8 (30.8%) patients were complicated with gallstone, 3(11.5%) patients with diabetes and 3(11.5%) patients with hypertension. Moreover, 2 (7.7%), 8 (30.8%), and 16 (61.5%) patients had the tumor size of <3cm, 3-5 and ≥5cm respectively. Besides, 9 (34.6%), 5 (19.2%), 4(15.4%) and 8(30.8%) patients were in T1, T2, T3 and T4, respectively. In addition, 14(53.8%) and 12(46.2%) candidates were in N0 and N1 Further, 21(80.8%) and 5(19.2%) patients were in M0 and M1. Finally, 8 (31.0%), 8 (31.0%), 5(19.2%) and 5(19.2%) patients were in stage I, stage II, IIIA and IV of the TNM stage, separately.

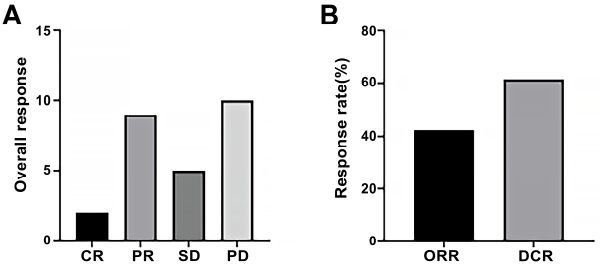

Fig. 1: Responsiveness of the patients to the therapy. A. CR, PR, SD and PD. B. ORR as well as DCR.

Overall response of the patients to the treatment

For all 26 patients enrolled in current work, 2 achieved CR, 9 achieved PR and 5 achieved SD. Moreover, 10 patients came to the progressed disease (PD) stage (fig. 1A). Furthermore, the ORR as well as DCR of the patients were 42.3% and 61.5%, respectively (fig. 1B). Moreover, the TNM stage of 16 patients showed successful downstaging while 10 patients did not show down staging (table 2).

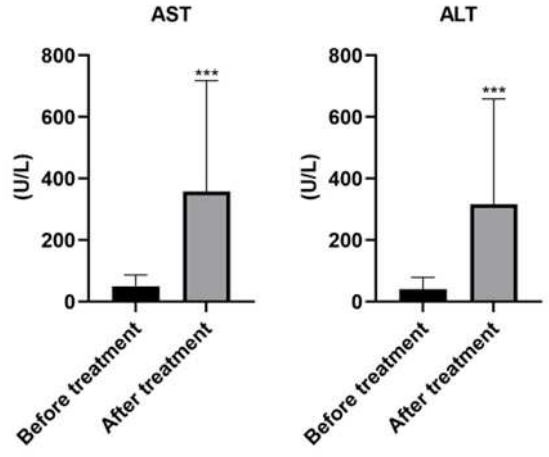

Fig. 2: AST and ALT of the patients.

Effects of the treatment on liver function of the patients

Next, the results of the routine blood test as well as the index for evaluating the liver function of the patients before and after treatment were compared. We found that the AST and ALT of the patients markedly increased after surgical resection plus camrelizumab (fig. 2, $p<0.05$).

Effects of the treatment on the prognosis of the patients

Finally, the effects of surgical resection plus camrelizumab on the prognosis of the patients have been evaluated. We found that the median value of the survival until the last day of the follow-up period was 7 (ranging from 1 to 23) months. The OS of the patients and the DFS was 76.9% and 69.2%, respectively (fig. 3A). Next, patients were divided into sensitive and non-sensitive to surgical resection plus camrelizumab groups based on whether they showed down staging. OS (fig. 3B, $p=0.0003$) as well as DFS (fig. 3B, $p<0.0001$) for sensitive group markedly increased compared with the non-sensitive group.

DISCUSSION

Our findings align with previous studies suggesting that PD-1 inhibitors significantly enhance survival rates in various cancer types post-surgical resection (Kong *et al*., 2022; Budimir *et al*., 2022; Li *et al*., 2022). Specifically, the combination of anti-PD-1/PD-L1 immunotherapy with surgery has demonstrated improved therapeutic efficacy in head and neck cancers (Botticelli *et al*., 2021). Similarly, in patients with resectable non-small cell lung cancer (NSCLC), PD-1 inhibitors have been shown to markedly increase pathological response rates with acceptable adverse effects (Forde *et al*., 2018). However, the efficacy of this approach in HCCA treatment has been less explored. Our study indicates that radical surgery and chemotherapy, in conjunction with the PD-1 inhibitor camrelizumab, not only show promising therapeutic effects but also significantly improve disease-free survival (DFS) and overall survival (OS) in HCCA patients.

Research on advanced cholangiocarcinoma treatment with immune checkpoint inhibitors has primarily been limited to later treatment lines or has involved immune medications alone. In a phase II non-randomized clinical trial with the immune checkpoint inhibitor CA209-538, which included 39 patients with advanced cholangiocarcinoma, 33 showed disease progression after first-line or multi-line treatments. The combination treatment of navulizumab and irilimumab resulted in an objective response rate (ORR) and disease control rate (DCR) of 23% and 44%, respectively (Klein *et al*., 2020). While these results are encouraging, they were specific to intrahepatic cholangiocarcinoma and gallbladder carcinoma, necessitating further validation in extrahepatic cholangiocarcinoma patients. Another phase II multi-center study reported median progression-free survival (PFS) and OS of 3.68 months and 14.24 months, respectively, for navulizumab monotherapy as a second- or third-line treatment for refractory cholangiocarcinoma patients, with an ORR of 22% and a DCR of 59%

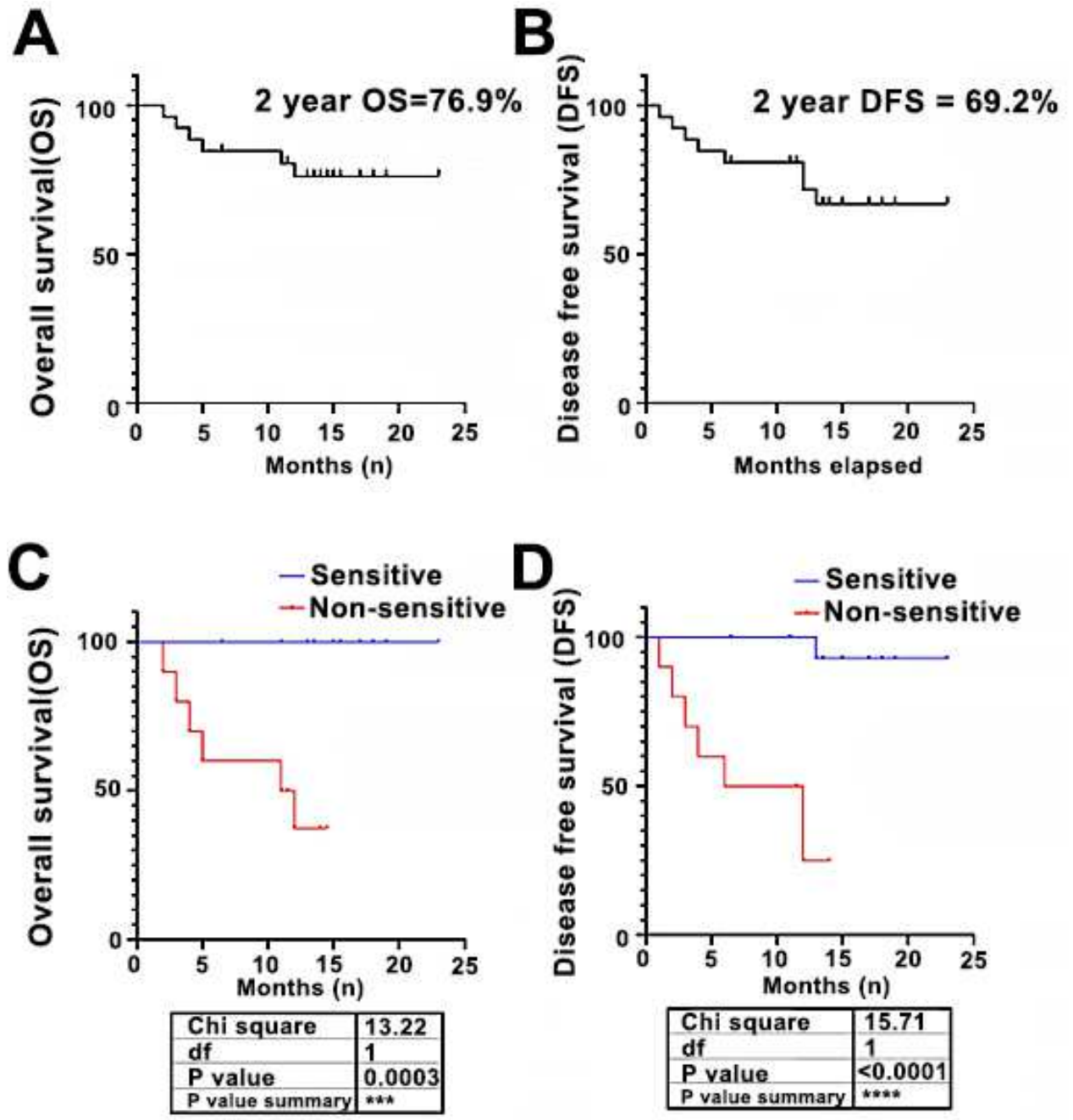

Fig. 3: Prognosis of the patients. A. The OS and DFS of the patients. B. Comparision of the survival of sensitive and non-sensitive patients.

(Edeline *et al*., 2020). The KEYNOTE-158 and KEYNOTE-966 studies further support the efficacy of pembolizumab in advanced-stage cholangiocarcinoma patients following standard first-line treatment (Marabelle *et al*., 2020; Kelley *et al*., 2023).

There is a dearth of research on the combination of immune checkpoint inhibitors and chemotherapy for cholangiocarcinoma management. Preliminary results from a study using navurizumab in combination with gemcitabine and cisplatin for unresectable or metastatic cholangiocarcinoma patients showed an ORR of 55.6% and a DCR of 92.6% (Rizvi *et al*., 2018). A phase I non-randomized multicenter study in Japan compared navulizumab monotherapy with the combination of navulizumab and standard first-line chemotherapy, revealing significantly higher ORR, PFS and OS in the combination group (Goyal *et al*., 2021). These findings underscore the potential of combining immune checkpoint inhibitors with chemotherapy as a more reliable and safe approach compared to monotherapy.

Table 2: TNM stage before and after treatment.

Items	HCCA patients (N=26)		P value
	Before treatment	After treatment	
TNM stage			<0.001
I	8	12	
II	8	6	
IIIA	5	5	
IIIB	0	0	
IV	5	1	
Downstaging, n(%)			
Success		16	
Failure		10	

In our study, radical surgery plus PD-1 inhibitors and chemotherapy resulted in a median OS of 7 months, with 2-year OS and DFS rates of 76.9% and 69.2%, respectively, in HCCA patients. Notably, patients who achieved down staging exhibited significantly improved DFS and OS compared to those who did not. This suggests that successful down staging may correlate with better tumor remission status and reduced recurrence, thereby increasing survival rates. Additionally, our study's liver function test results indicated a marked increase in liver and gallbladder function following treatment with surgical resection and camrelizumab. Collectively, these results suggest that the combination of radical surgery, chemotherapy, and PD-1 inhibitor camrelizumab is efficacious for HCCA treatment.

Despite the significance of our findings, our study has limitations. Firstly, the sample size is small, and all patients are from the Southwest region of China, which may limit the generalizability of our results. Future studies should include larger sample sizes and patients from diverse geographical locations. Secondly, our study lacked a control group, which is a critical component for future research to strengthen the validity of our findings.

CONCLUSION

Our study suggests that radical surgery, chemotherapy and PD-1 inhibitor camrelizumab may serve as effective and safe treatment options for HCCA. While further investigations are warranted, our findings offer a novel approach for the clinical management of HCCA.

ACKNOWLEDGMENTS

We thank all the patients and their families for participation in the present study.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this document.

REFERENCES

Anderson B and Doyle MBM (2019). Surgical Considerations of Hilar Cholangiocarcinoma. *Surg. Oncol. Clin. N. Am.*, **28**(4): 601-617.

Botticelli A, Cirillo A, Strigari L, Valentini F, Cerbelli B, Scagnoli S, Cerbelli E, Zizzari IG, Rocca CD, D'Amati G, Polimeni A, Nuti M, Merlano MC, Mezi S and Marchetti P (2021). Anti-PD-1 and anti-PD-L1 in head and neck cancer: A network meta-analysis. *Front Immunol.*, **12**: 705096.

Budimir N, Thomas GD, Dolina JS and Salek-Ardakani S (2022). Reversing T-cell exhaustion in cancer: Lessons learned from PD-1/PD-L1 immune checkpoint blockade. *Cancer Immunol. Res.*, **10**(2): 146-153.

Edeline J, Touchefeu Y, Guiu B, Farge O, Tougeron D, Baumgaertner I, Ayav A, Campillo-Gimenez B, Beuzit L, Pracht M, Lièvre A, Le Sourd S, Boudjema K, Rolland Y, Boucher E and Garin E (2020). Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: A phase 2 clinical trial. *JAMA Oncol.*, **6**(1): 51-59.

Elvevi A, Laffusa A, Scaravaglio M, Rossi RE, Longarini R, Stagno AM, Cristoferi L, Ciaccio A, Cortinovis DL, Invernizzi P and Massironi S (2022). Clinical treatment of cholangiocarcinoma: An updated comprehensive review. *Ann. Hepatol.*, **27**(5): 100737.

Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD, Zahurak M, Yang SC, Jones DR, Broderick S, Battafarano RJ, Velez MJ, Rekhtman N, Olah Z, Naidoo J, Marrone KA, Verde F, Guo H, Zhang J, Caushi JX, Chan HY, Sidhom JW, Scharpf RB, White J, Gabrielson E, Wang H, Rosner GL, Rusch V, Wolchok JD, Merghoub T, Taube JM, Velculescu VE, Topalian SL, Brahmer JR and Pardoll DM (2018). Neoadjuvant PD-1 blockade in resectable lung cancer. *N. Engl. J. Med.*, **378**(21): 1976-1986.

Goyal L, Kongpetch S, Crolley VE and Bridgewater J (2021). Targeting FGFR inhibition in cholangiocarcinoma. *Cancer Treat. Rev.*, **95**: 102170.

Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, Yau T, Klümpen HJ, Chan SL, Ozaka M, Verslype C, Bouattour M, Park JO, Barajas O, Pelzer U, Valle JW, Yu L, Malhotra U, Siegel AB, Edeline J, Vogel A and KEYNOTE-966 Investigators (2023). Pembrolizumab in combination with gemcitabine and cisplatin

compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.*, **401**(10391): 1853-1865.

Klein O, Kee D, Nagrial A, Markman B, Underhill C, Michael M, Jackett L, Lum C, Behren A, Palmer J, Tebbutt NC, Carlino MS and Cebon J (2020). Evaluation of combination nivolumab and ipilimumab immunotherapy in patients with advanced biliary tract cancers: subgroup analysis of a phase 2 nonrandomized clinical trial. *JAMA Oncol.*, **6**(9): 1405-1409.

Kong Y, Zhao X, Xu M, Pan J, Ma Y, Zou L, Peng Q, Zhang J, Su C, Xu Z, Zhou W, Peng Y, Yang J, Zhou C, Li Y, Guo Q, Chen G, Wu H, Xing P and Zhang L (2022). PD-1 inhibitor combined with radiotherapy and gm-csf (prag) in patients with metastatic solid tumors: An open-label phase II study. *Front Immunol.*, **13**: 952066.

Lee JW, Zhang Y, Yoshizawa T, Argani P, Wood LD and Oshima K (2022). Cancerization of ducts in hilar cholangiocarcinoma. *Virchows. Arch.*, **481**(2): 1-10.

Li Q, Han J, Yang Y and Chen Y (2022). PD-1/PD-L1 checkpoint inhibitors in advanced hepatocellular carcinoma immunotherapy. *Front Immunol.*, **13**: 1070961.

Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK and Diaz LA (2020). Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 Study. *J. Clin. Oncol.*, **38**(1):1-10.

Quinn LM, Haldenby S, Antzcak P, Fowler A, Bullock K, Kenny J, Gilbert T, Andrews T, Diaz-Nieto R, Fenwick S, Jones R, Costello-Goldring E, Poston G, Greenhalf W, Palmer D, Malik H and Goldring C (2023). Genomic profiling of idiopathic peri-hilar cholangiocarcinoma reveals new targets and mutational pathways. *Sci. Rep.*, **13**(1): 6681.

Rizvi S, Khan SA, Hallemeier CL, Kelley RK and Gores GJ (2018). Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat. Rev. Clin. Oncol.*, **15**(2): 95-111.

Sapisochin G, Ivanics T, Subramanian V, Doyle M, Heimbach JK and Hong JC (2020). Multidisciplinary treatment for hilar and intrahepatic cholangiocarcinoma: A review of the general principles. *Int. J. Surg.*, **82S**: 77-81.

Soares KC and Jarnagin WR (2021). The Landmark Series: Hilar Cholangiocarcinoma. *Ann. Surg. Oncol.*, **28**(8): 4158-4170.

Xia T, Li K, Niu N, Shao Y, Ding D, Thomas DL, Jing H, Fujiwara K, Hu H, Osipov A, Yuan C, Wolfgang CL, Thompson ED, Anders RA, He J, Mou Y, Murphy AG and Zheng L (2022). Immune cell atlas of cholangiocarcinomas reveals distinct tumor microenvironments and associated prognoses. *J. Hematol. Oncol.*, **15**(1): 37.

Zhang MY, Luo M and Wang JP (2022). FXR expression in rats of hilar cholangiocarcinoma. *Sci. Rep.*, **12**(1): 8741.

Zhang MY, Wang JP, He K and Xia XM (2021). Bsep expression in hilar cholangiocarcinoma of rat model. *Sci. Rep.*, **11**(1): 2861.

Zhao Q, Chen Y, Du S, Yang X, Chen Y, Ji Y and Zeng Z (2021). Integration of radiotherapy with anti-PD-1 antibody for the treatment of intrahepatic or hilar cholangiocarcinoma: Reflection from four cases. *Cancer Biol. Ther.*, **22**(3): 175-183.