IN VIVO *39*: 1724-1730 (2025)
doi: 10.21873/invivo.13974

Conversion Surgery Performed Following Durvalumab Combined With Gemcitabine and Cisplatin in Cholangiocarcinoma: A Case Report

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Abstract

Background/Aim: Immunotherapy using immune checkpoint inhibitors (ICIs) has been widely approved for many cancers. ICI therapy has also been performed for unresectable bile duct cancer in recent years. However, there are few reports of conversion surgery following ICI therapy for unresectable or borderline resectable bile duct cancer. Herein, we present a case of conversion surgery following immune checkpoint ICI therapy for unresectable cholangiocarcinoma, focusing on the cancer immune microenvironment of this case.

Case Report: A 77-year-old man was diagnosed with borderline resectable, distal bile duct cancer and hilar cholangiocarcinoma. The patient underwent four courses of durvalumab combined with gemcitabine and cisplatin (Dur+GC) therapy. Evaluation of disease progression showed stable disease (SD), and considering the patient's surgical risk, a pancreaticoduodenectomy was performed. Adenocarcinoma components remained, and detailed pathological examinations using immunohistochemistry were performed. Marked infiltration of lymphocytes was observed in both the cancer core area and the margin area. The lymphocytes were positive for CD3 and CD8, with a subset also expressing CD103. PD-L1 expression was weakly positive in the stromal area, and positive cells were likely to be infiltrating macrophages in morphological features. Cancer cells were positive for HLA-A/B/C and beta-2.

Conclusion: CD103+ CD8+ T cells, recently referred to as tissue-resident memory T cells, might be a critical immune cell population involved in ICI-induced anticancer immune responses in cholangiocarcinoma.

Keywords: Prognostic biomarker, immune checkpoint inhibitor, tumor-infiltrating lymphocytes, bile duct cancer.

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Received January 20, 2025 | Revised February 22, 2025 | Accepted March 4, 2025

Introduction

Cholangiocarcinoma is an aggressive malignant cancer originating from the biliary epithelium (1, 2). Extrahepatic cholangiocarcinoma (ECC) accounts for approximately 20-30% of all cholangiocarcinomas, and its prognosis remains poor, with an estimated 5-year survival rate of 11% (localized and regional: 18%; distant: 2%) (3, 4). For non-metastatic ECC, surgery remains the only curative treatment. However, less than one-third of cholangiocarcinoma patients are diagnosed at a stage amenable to surgical resection, with the majority being deemed unresectable or presenting with recurrent disease, both associated with a poor prognosis (5-8).

For over a decade, the combination of gemcitabine and cisplatin has been the standard first-line chemotherapy regimen for advanced biliary tract cancer (9), with a median overall survival ranging from 4.6 to 11.7 months (10). The TOPAZ-1 trial demonstrated that the addition of the immune checkpoint inhibitor (ICI) durvalumab to the gemcitabine-cisplatin regimen improved overall survival compared with gemcitabine-cisplatin alone (11).

A case in which the combination therapy of durvalumab and gemcitabine-cisplatin (Dur+GC) was effective, leading to conversion surgery, is reported. The resected cholangiocarcinoma specimen underwent detailed pathological examination using immunohistochemistry.

Case Report

A 77-year-old male presented with darkened urine and was referred for further evaluation due to obstructive jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) and cholangioscopy showed strictures at both the distal bile duct and the hilar region, with biopsy confirming adeno-carcinoma at both sites (Figure 1). No cancer cells were detected in the bile duct between the hilar and distal sites. Contrast-enhanced computed tomography (CT) showed mural thickening in the distal bile duct, with a tumor depth suggesting invasion into the pancreatic parenchyma (approximately 10 mm). In addition, mural thickening was observed in the right hepatic duct extending to the upper common bile duct. No liver metastases, distant metastases, or significant lymphadenopathy was found. A diagnosis of distal bile duct cancer (cT2N0M0, cStage II) and hilar cholangiocarcinoma Bismuth IIIa (cT2aN0M0, cStage II) was established.

The initial treatment goal was to perform an extended right hepatectomy combined with pancreatico-duodenectomy. Laparoscopic exploration showed no evidence of peritoneal dissemination or distant metastasis, and peritoneal lavage cytology was negative. Portal vein embolization was performed to increase future liver remnant volume. Due to tumor involvement at the resection margins, four courses of Dur+GC were administered. Tumor response was assessed as stable disease (SD) according to RECIST criteria. The National Clinical Database (NCD) risk calculator indicated a perioperative mortality risk of 12.2% for hepato-pancreatoduodenectomy (HPD), categorizing the procedure as high-risk. After discussion with the patient and family, a decision was made to proceed with pancreaticoduodenectomy alone, followed by postoperative radiotherapy and chemotherapy for remaining disease. Eight weeks after the final administration of Dur+GC, pancreaticoduodenectomy was performed.

Pathological examination showed a moderately differentiated adenocarcinoma with areas of both poorly and well-differentiated components (ypT2N0M0, ypStage II). The tumor exhibited a flat invasive pattern, infiltrating the bile duct wall, pancreatic parenchyma, duodenum, and the ampulla of Vater, with an invasion depth of 10 mm. Venous invasion, lymphatic invasion, and perineural invasion were noted. The surgical margins were negative, and no lymph node metastases were detected. Postoperatively, the patient experienced chyle leakage that required several drain exchanges, but he was ultimately discharged in good condition. The patient continues postoperative treatment with gemcitabine, cisplatin, and S-1.

Pathological examinations using resected specimens. With routinely prepared hematoxylin and eosin staining, marked lymphocyte infiltration was observed in the

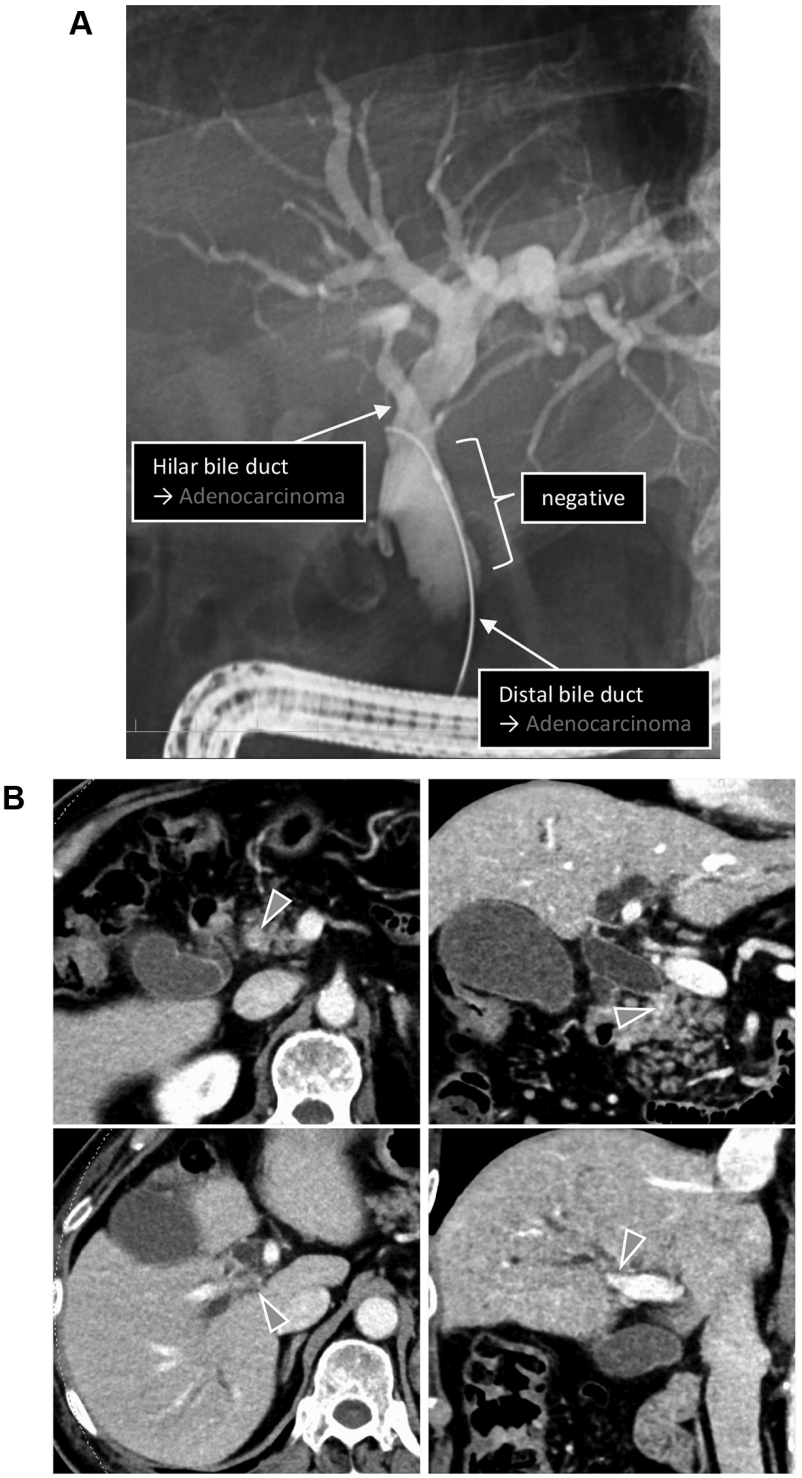

Figure 1. *Preoperative endoscopic retrograde cholangiopancreatography image (A) shows adenocarcinoma in the hilar and distal bile ducts confirmed by biopsy. The arrows indicate the site of the biopsy in the bile duct. Contrast-enhanced computed tomography (B) shows solid mural thickening in the same regions. The arrowheads indicate the areas where findings suggestive of bile duct cancer are present.*

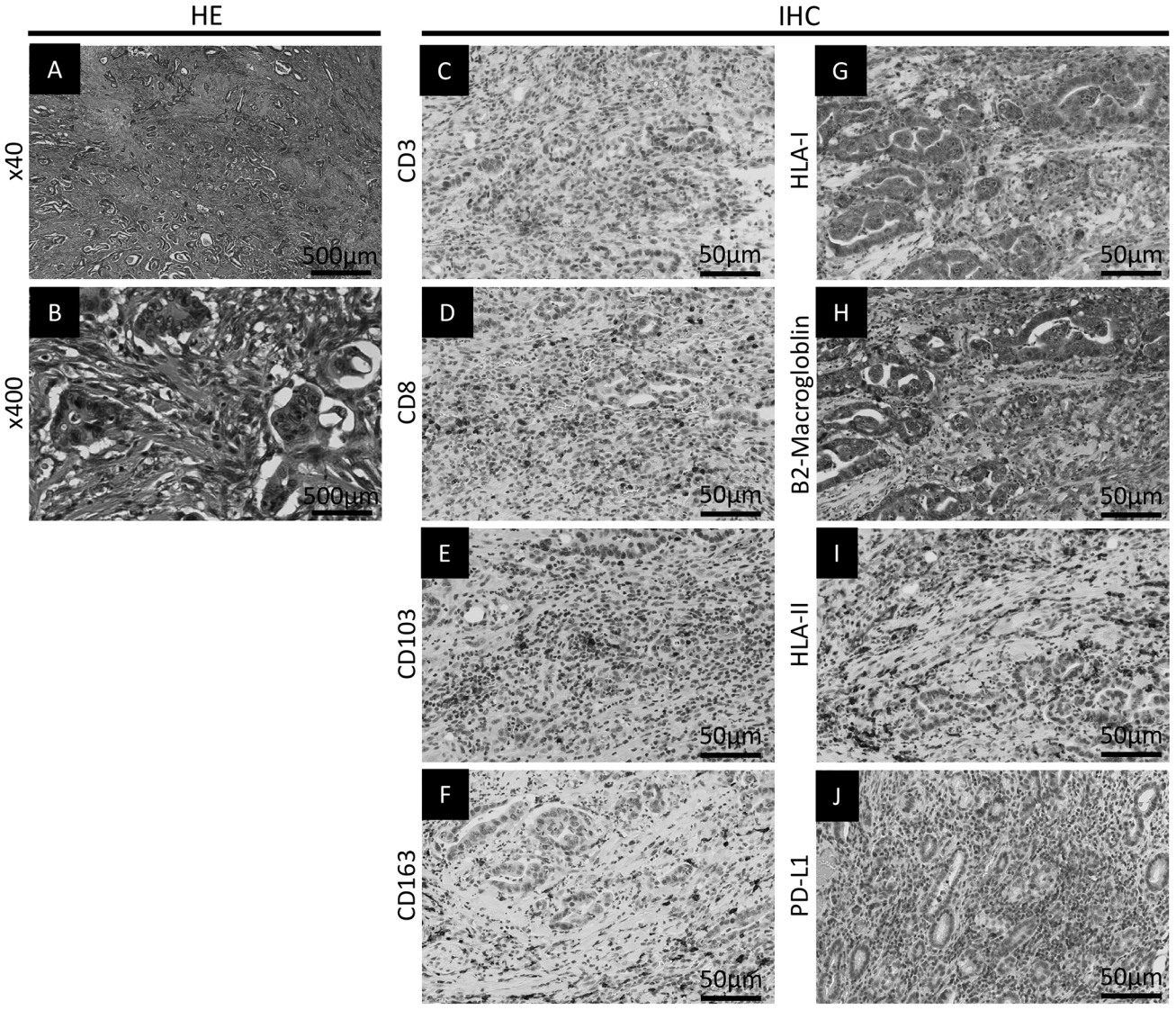

Figure 2. *Pathological examinations, hematoxylin and eosin (HE) staining and immunohistochemical (IHC) staining. IHC of HLA-A/B/C, HLA-DR, CD3, CD8, CD103, CD163 and beta-2 microglobulin was performed as described previously (23). Scale bar: 500 μm in (A) 50 μm in (B-I).*

stromal area in which viable adenocarcinoma components remained (Figure 2). Then, the immunological characteristics of lymphocytes and cancer cells were examined, as shown in Figure 2. Similar notable lymphocyte infiltration was seen in both the cancer core and the invasive margin area, and many of the lymphocytes were positive for CD3 (201 cells/mm^2), CD8 (190 cells/mm^2), and CD103 (117 cells/mm^2); CD8 and CD103 appeared positive in around half of CD3-positive T cells. PD-L1 expression was predominantly observed in stromal cells, likely macrophages. HLA-A/B/C and beta-2 microglobulin were positive in almost all cancer cells, with no HLA-DR expression seen in cancer cells.

Approval for human experiments. The study design was approved by the Institutional Review Board of Kumamoto

University (Approval No. #2059) in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The need for individual patient consent for participation in the study was waived by the Institutional Review Board of Kumamoto University (Approval No. #2059) as the study was a retrospective analysis. However, patients were provided the opportunity to opt out of the study.

Discussion

In non-metastatic ECC, surgery remains the only curative treatment. However, advanced T-stage, lymphovascular invasion, or perineural invasion are significant risk factors for local and distant recurrence following curative resection (12). In the present case, adenocarcinoma was identified in multiple segments of the bile duct. Given the extent of the disease and the patient's surgical risk, the tumor was classified as borderline resectable to unresectable, prompting treatment with Dur+GC. Reports of conversion surgery following ICI therapy for unresectable or borderline-resectable bile duct cancer are scarce, and pathological analyses of resected specimens post-ICI therapy are not well-documented. PD-L1-targeted treatment regimens disrupt the inhibitory signaling pathways in T cells, restoring cytolytic activity and promoting tumor cell killing (13). Though some patients with cholangiocarcinoma demonstrate robust anticancer responses to such regimens, the response varies, and reliable predictive biomarkers for ICI efficacy are still lacking.

CD8+ T cell-mediated immune surveillance plays a critical role in sustained cancer resistance and outcomes (14), with a significant impact noted in intrahepatic cholangiocarcinoma (ICC) (15). Tumor-infiltrating lymphocytes (TILs) have been associated with prognosis in ICC, where higher CD8+ infiltration correlated with improved survival and lower recurrence rates (16). In ECC, Kitano *et al.* reported that CD8+ lymphocyte infiltration serves as an independent prognostic factor (17). However, PD-1 and PD-L1 expression on immune cells did not significantly affect overall survival (OS) (17).

In the present case, abundant CD8+ TILs were observed in both the tumor core and margin following ICI therapy. Notably, PD-L1 expression was prominent at the tumor margin. In melanoma, CD103+ CD8+ T cells within the tumor microenvironment (TME) have been shown to upregulate inhibitory checkpoints such as PD-1, CTLA-4, TIM-3, LAG-3, TIGIT, and CD39, indicating their role as tumor antigen-reactive T cells (18-20). Tissue-resident CD103+ T cells are key effector cells in localized antitumor immune responses and response to anti-PD-1 therapy (21). They have been identified as a potential quantifiable marker for predicting patient survival across various solid tumors (18), including ICC, where higher CD103+ CD8+ expression was associated with better OS (22). In the present case, nearly 50% of CD8+ T cells expressed CD103, indicating tissue residency. This suggests that the presence of these cells may contributed to effective disease control during the period of ICI therapy prior to surgery.

Conclusion

A case of borderline resectable ECC was managed with Dur+GC therapy, followed by conversion surgery. Increased lymphocyte infiltration may serve as a potential predictive marker for the efficacy of ICI therapy in cholangiocarcinoma as well as other several cancers. CD103+ CD8+ T cell, recently referred as tissue-resident memory T cell, is suggested to be involved in ICI-induced anticancer immune responses in cholangiocarcinoma.

Conflicts of Interest

All Authors have no conflicts of interest related to this manuscript.

Authors' Contributions

Yoshiyuki Tagayasu: Collected clinical data of the case, performed histological and immunohistochemical analyses, drafted the manuscript, and contributed to data analysis. Rin Yamada: Conducted histological and immunohistochemical

analyses and contributed to data interpretation. Kosuke Kanemitsu: Assisted in the design of the study. Yoshihiko Kondo: Supported histological and immunohistochemical analyses. Rumi Itoyama: Assisted in analyzing case data and documenting clinical progress. Hiromitsu Hayashi: Coordinated the diagnosis and treatment strategies and supported the surgical procedures. Yoshihiro Komohara: Supervised the entire study and reviewed and approved the final manuscript. Masaaki Iwatsuki: Managed the case and supervised the overall study.

Acknowledgements

We thank K.I. Stainer Inc. (Kumamoto, Japan) for their technical assistance. This work was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 20H03459).

References

1 Dar FS, Abbas Z, Ahmed I, Atique M, Aujla UI, Azeemuddin M, Aziz Z, Bhatti ABH, Bangash TA, Butt AS, Butt OT, Dogar AW, Farooqi JI, Hanif F, Haider J, Haider S, Hassan SM, Jabbar AA, Khan AN, Khan MS, Khan MY, Latif A, Luck NH, Malik AK, Rashid K, Rashid S, Salih M, Saeed A, Salamat A, Tayyab GU, Yusuf A, Zia HH, Naveed A: National guidelines for the diagnosis and treatment of hilar cholangiocarcinoma. World J Gastroenterol 30(9): 1018-1042, 2024. DOI: 10.3748/wjg.v30.i9.1018

2 Rushbrook SM, Kendall TJ, Zen Y, Albazaz R, Manoharan P, Pereira SP, Sturgess R, Davidson BR, Malik HZ, Manas D, Heaton N, Prasad KR, Bridgewater J, Valle JW, Goody R, Hawkins M, Prentice W, Morement H, Walmsley M, Khan SA: British Society of Gastroenterology guidelines for the diagnosis and management of cholangiocarcinoma. Gut 73(1): 16-46, 2023. DOI: 10.1136/gutjnl-2023-330029

3 Ali H, Zweigle J, Patel P, Tedder B, Khan R, Agrawal S: Survival analysis of extrahepatic cholangiocarcinoma based on surveillance, epidemiology, and end results database. Ann Hepatobiliary Pancreat Surg 27(2): 151-157, 2023. DOI: 10.14701/ahbps.22-090

4 Razumilava N, Gores GJ: Cholangiocarcinoma. Lancet 383(9935): 2168-2179, 2014. DOI: 10.1016/S0140-6736(13)61903-0

5 Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS: Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. Cancer 122(9): 1349-1369, 2016. DOI: 10.1002/cncr.29692

6 Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM: Treatment and prognosis for patients with intrahepatic cholangiocarcinoma. JAMA Surg 149(6): 565, 2014. DOI: 10.1001/jamasurg.2013.5137

7 Waisberg DR, Pinheiro RS, Nacif LS, Rocha-Santos V, Martino RB, Arantes RM, Ducatti L, Lai Q, Andraus W, D'Albuquerque LC: Resection for intrahepatic cholangiocellular cancer: new advances. Transl Gastroenterol Hepatol 3: 60, 2018. DOI: 10.21037/tgh.2018.08.03

8 Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX: Biliary tract cancer. Lancet 397(10272): 428-444, 2021. DOI: 10.1016/S0140-6736(21)00153-7

9 Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362(14): 1273-1281, 2010. DOI: 10.1056/NEJMoa0908721

10 Park JO, Oh DY, Hsu C, Chen JS, Chen LT, Orlando M, Kim JS, Lim HY: Gemcitabine plus cisplatin for advanced biliary tract cancer: a systematic review. Cancer Res Treat 47(3): 343-361, 2015. DOI: 10.4143/crt.2014.308

11 Rimini M, Fornaro L, Lonardi S, Niger M, Lavacchi D, Pressiani T, Lucchetti J, Giordano G, Pretta A, Tamburini E, Pirrone C, Rapposelli IG, Diana A, Martinelli E, Garajová I, Simionato F, Schirripa M, Formica V, Vivaldi C, Caliman E, Rizzato MD, Zanuso V, Nichetti F, Angotti L, Landriscina M, Scartozzi M, Ramundo M, Pastorino A, Daniele B, Cornara N, Persano M, Gusmaroli E, Cerantola R, Salani F, Ratti F, Aldrighetti L, Cascinu S, Rimassa L, Antonuzzo L, Casadei-Gardini A: Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: An early exploratory analysis of real-world data. Liver Int 43(8): 1803-1812, 2023. DOI: 10.1111/liv.15641

12 Ethun CG, Le N, Lopez-Aguiar AG, Pawlik TM, Poultsides G, Tran T, Isom CA, Fields RC, Krasnick BA, Weber SM, Salem A, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Russell MC, Maithel SK: Pathologic and prognostic implications of incidental *versus* nonincidental gallbladder cancer: A 10-institution Study from the United States Extrahepatic Biliary Malignancy Consortium. Am Surg 83(7): 679-686, 2017.

13 Pauken KE, Wherry EJ: Overcoming T cell exhaustion in infection and cancer. Trends Immunol 36(4): 265-276, 2015. DOI: 10.1016/j.it.2015.02.008

14 Beura LK, Mitchell JS, Thompson EA, Schenkel JM, Mohammed J, Wijeyesinghe S, Fonseca R, Burbach BJ, Hickman HD, Vezys V, Fife BT, Masopust D: Intravital mucosal imaging of CD8(+) resident memory T cells shows tissue-autonomous recall responses that amplify secondary memory. Nat Immunol 19(2): 173-182, 2018. DOI: 10.1038/s41590-017-0029-3

15 Fabris L, Perugorria MJ, Mertens J, Björkström NK, Cramer T, Lleo A, Solinas A, Sänger H, Lukacs-Kornek V, Moncsek A, Siebenhüner A, Strazzabosco M: The tumour microenvironment and immune milieu of cholangiocarcinoma. Liver Int 39 (Suppl 1): 63-78, 2019. DOI: 10.1111/liv.14098

16 Vigano L, Soldani C, Franceschini B, Cimino M, Lleo A, Donadon M, Roncalli M, Aghemo A, Di Tommaso L, Torzilli G: Tumor-infiltrating lymphocytes and macrophages in intrahepatic cholangiocellular carcinoma. impact on prognosis after complete surgery. J Gastrointest Surg 23(11): 2216-2224, 2019. DOI: 10.1007/s11605-019-04111-5
17 Kitano Y, Okabe H, Yamashita YI, Nakagawa S, Saito Y, Umezaki N, Tsukamoto M, Yamao T, Yamamura K, Arima K, Kaida T, Miyata T, Mima K, Imai K, Hashimoto D, Komohara Y, Chikamoto A, Ishiko T, Baba H: Tumour-infiltrating inflammatory and immune cells in patients with extrahepatic cholangiocarcinoma. Br J Cancer 118(2): 171-180, 2018. DOI: 10.1038/bjc.2017.401
18 Byrne A, Savas P, Sant S, Li R, Virassamy B, Luen SJ, Beavis PA, Mackay LK, Neeson PJ, Loi S: Tissue-resident memory T cells in breast cancer control and immunotherapy responses. Nat Rev Clin Oncol 17(6): 341-348, 2020. DOI: 10.1038/s41571-020-0333-y
19 Lin R, Zhang H, Yuan Y, He Q, Zhou J, Li S, Sun Y, Li DY, Qiu HB, Wang W, Zhuang Z, Chen B, Huang Y, Liu C, Wang Y, Cai S, Ke Z, He W: Fatty acid oxidation controls CD8+ tissue-resident memory T-cell survival in gastric adenocarcinoma. Cancer Immunol Res 8(4): 479-492, 2020. DOI: 10.1158/2326-6066.CIR-19-0702
20 Kumagai S, Togashi Y, Kamada T, Sugiyama E, Nishinakamura H, Takeuchi Y, Vitaly K, Itahashi K, Maeda Y, Matsui S, Shibahara T, Yamashita Y, Irie T, Tsuge A, Fukuoka S, Kawazoe A, Udagawa H, Kirita K, Aokage K, Ishii G, Kuwata T, Nakama K, Kawazu M, Ueno T, Yamazaki N, Goto K, Tsuboi M, Mano H, Doi T, Shitara K, Nishikawa H: The PD-1 expression balance between effector and regulatory T cells predicts the clinical efficacy of PD-1 blockade therapies. Nat Immunol 21(11): 1346-1358, 2020. DOI: 10.1038/s41590-020-0769-3
21 Edwards J, Wilmott JS, Madore J, Gide TN, Quek C, Tasker A, Ferguson A, Chen J, Hewavisenti R, Hersey P, Gebhardt T, Weninger W, Britton WJ, Saw RP, Thompson JF, Menzies AM, Long GV, Scolyer RA, Palendira U: CD103+ tumor-resident CD8+ T cells are associated with improved survival in immunotherapy-naïve melanoma patients and expand significantly during anti–PD-1 treatment. Clin Cancer Res 24(13): 3036-3045, 2018. DOI: 10.1158/1078-0432.CCR-17-2257
22 Chen L, Huang H, Huang Z, Chen J, Liu Y, Wu Y, Li A, Ge J, Fang Z, Xu B, Zheng X, Wu C: Prognostic values of tissue-resident CD8(+)T cells in human hepatocellular carcinoma and intrahepatic cholangiocarcinoma. World J Surg Oncol 21(1): 124, 2023. DOI: 10.1186/s12957-023-03009-6
23 Arima K, Komohara Y, Uchihara T, Yamashita K, Uemura S, Hanada N, Baba H: A case of mesenteric desmoid tumor causing bowel obstruction after laparoscopic surgery. Anticancer Res 42(1): 381-384, 2022. DOI: 10.21873/anticanres.15496