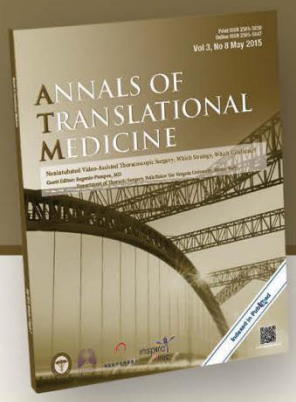
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-4698

Reviewer A

Despite there are several articles about this topic in literature, the authors present the first comprehensive systemic review to compare the clinicopathologic characteristics, perioperative indices and postoperative OS between HCC patients with and without BDTT.
The study is well structured and well conducted, with a superb statistical analysis.
The PRISMA statement is included.
REFERENCES are OK
TABLEES are exhaustive.
LANGUAGE: Minor language polishing is needed…

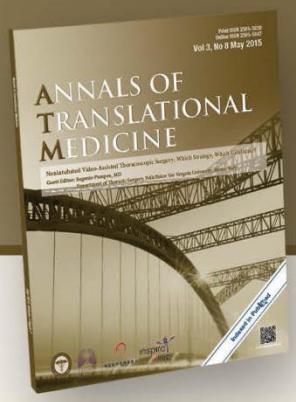
Reply to Reviewer A:

Thank you very much for your high appraisal and favorable opinions of our work. We have presented the first comprehensive systematic review and meta-analysis, which included the largest target study population to date, to compare the clinicopathological characteristics, perioperative indices and postoperative long-term survival outcomes between HCC patients with BDTT and without BDTT. Furthermore, we have explored the prognostic significance of BDTT on HCC.

The results revealed that the levels of total bilirubin and alkaline phosphatase were significantly higher in HCC patients with BDTT, whereas the liver functional status was markedly better in patients without BDTT. Aggressive biological features, such as poor tumor differentiation, macroscopic invasion (PVTT, HVTT) and lymph node metastasis were more frequently encountered in patients with HCC and BDTT. The 1-year, 3-year and 5-year overall survival (OS) were significantly worse in HCC patients with BDTT versus those without BDTT. The hazard ratio (HR) of HCC with BDTT was 4.27 (95% CI = 3.47-5.26, $P < 0.01$) within 5 years following hepatectomy.

Although well organized, logistically sound and well structured, we have to admit that this meta-analysis has its own intrinsic defect and drawbacks. Because all of the studies included were retrospective observational studies, the baseline clinical and pathological characteristics of these two comparative groups (the BDTT and non-BDTT groups) were not well-balanced. So, it can be analyzed and concluded that HCC patients with BDTT are more likely to be at more advanced stage of disease. In this study, because of the scarcity of adjusted multivariate HRs reported in the original studies, we mainly extracted HRs from the only available survival curves, the significance of which basically equals to the value of unadjusted univariate HRs, which do not preclude the impact of other potential co-variates and confounders. Unfortunately, this cannot be resolved using varieties of statistical algorithm like subgroup analysis or meta-regression analysis due to the intrinsic heterogeneity across studies. Hence, “The hazard ratio of HCC with BDTT was 4.27 within 5 years following hepatectomy.” and “BDTT may be a prognostic factor for HCC patients.” should be interpreted with cautious.

ANNALS OF TRANSLATIONAL MEDICINE



As to the primary concern of you reviewer, we have polished the whole manuscript and modified the incorrect usage of language under the guidance of an external linguistic expert, who specializes in professional English and in the field of oncological studies.

Again, we would like to express our thankfulness to you one more time for your positive comment and acknowledgment of our study. We hope that the revised manuscript is now suitable for publication in Annals of Translational Medicine.

Reviewer B

The authors presented a systematic review focusing clinical impact of biliary ductal tumor thrombus (BDTT) of hepatocellular carcinoma (HCC) on prognosis after curative hepatectomy. The systematic review was completed according to PRISMA statement. The Methodology was sound and limitations of the current study were also documented in Discussion. I have few questions for the work.

Major points:

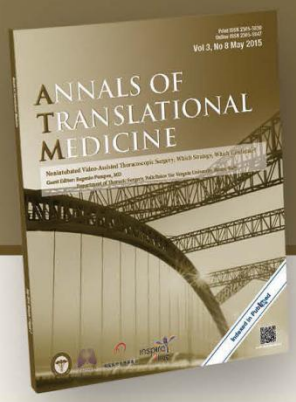
1. The definition of BDTT should be described more specifically. Does it include any invasion of HCC into bile duct with or without obstruction of bile duct? Does it include pathological microscopic BDTT inside HCC capsule?

Reply to Reviewer B:

Thanks for your nice suggestions and good recommendations. We have carefully reviewed all of the 15 studies again, and made a specific definition of BDTT as "BDTT is defined as an intraductal neoplasm, which consists of HCC cells and lining biliary epithelial cells under microscope", which have been added in the second paragraph of the "Introduction" section (**see Page 4, line 9–10**).

Typically, when BDTT extends beyond the confluence of the left and right hepatic ducts, patients with HCC and BDTT will manifest with the symptoms of obstructive jaundice. **As to the first question of the major points 1**, actually, we **have included patients with any invasion of HCC into BDTT, regardless of whether the biliary tract is obstructed by tumor thrombus**. The facts can be indirectly reflected in the numbers (or percentages) of patients with or without obstructive jaundice reported in each of the study.

As to the second question of the major points 1, we **indeed included HCC patients with peripheral microscopic BDTT**. However, macro- and microscopic BDTT were defined not on the basis of the relationship of BDTT with adjacent HCC capsule, **but rather on the anatomic location of BDTT in the biliary systems**. According to the *Liver Cancer Study Group of Japan* (1), BDTT can be classifies as the following four types: B1 (invasion of the third order or more peripheral branches of the bile duct, but not of second order branches); B2 (invasion of the second order branches of the bile duct); B3 (invasion of the first order branches of the bile duct); B4 (invasion of the common hepatic duct or the common bile duct). Based on the exploratory findings intraoperatively and pathological examinations postoperatively, BDTT in most of the included studies can simply be categorized as macroscopic (B2–B4) and microscopic BDTT (B1) according to the proposition by Esaki et al (2).



In order to respond to the two above concerns that you have raised, we have added a supplementary table (**see Supplementary Table 1**) as the supporting material to show the detailed information of the BDTT group of patients, which consists of (1) the detailed number of patients with either microscopic BDTT or macroscopic BDTT; (2) the particular number of patients with or without obstructive jaundice; (3) the specific definition of macro- and microscopic BDTT in the included studies (**see Page 6, line 16–19**). Additionally, the contents exhibited in the Supplementary Table 1 are expressed in the part of "basic characteristics and methodologic quality" under the section of Results (**see Page 8, line 13–20**).

References:

1. Kudo M, Kitano M, Sakurai T, et al. General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: the outstanding achievements of the Liver Cancer Study Group of Japan. Dig Dis 2015; 33(6):765-70.
2. Esaki M, Shimada K, Sano T, et al. Surgical results for hepatocellular carcinoma with bile duct invasion: a clinicopathologic comparison between macroscopic and microscopic tumor thrombus. J Surg Oncol 2005; 90(4):226-32.

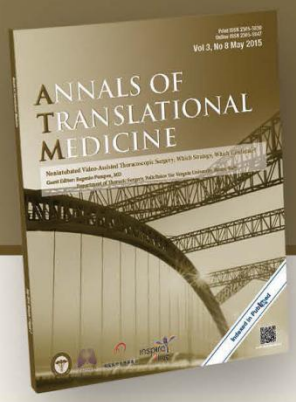
2. The current study excluded patients who underwent adjuvant therapy after hepatectomy. It might not being appropriate in clinical situation because prognosis of BDTT patients should be evaluated comprehensively including hepatectomy, neoadjuvant therapy and adjuvant therapy. The authors should describe the rationale to exclude patients with adjuvant therapy.

Reply to Reviewer B:

Thanks for your good questions and clinical considerations. Here, I totally agree with you that preoperative neoadjuvant treatment or postoperative adjuvant therapy has been widely performed in clinical settings, especially in China.

Neoadjuvant treatment, including preoperative transcatheter arterial chemoembolization (TACE) and radiotherapy (RT), is booming in recent years and gradually accepted by many clinical practitioners because of the concepts that the initially unresectable or inoperable tumor can be down-staged and converted to a stage where curative surgery can be performed and long-term survival can be anticipated thereafter. In the field of hepatocellular carcinoma (HCC), the safety and efficacy of neoadjuvant therapy have been repeatedly demonstrated (1–3). Our research team conducted a randomized, open-label, multicenter controlled study, which revealed that neoadjuvant three-dimensional conformal RT is beneficial for patients with resectable HCC with portal vein tumor thrombus (PVTT) (4).

Also, post-surgical anticancer treatment, also termed "postoperative adjuvant therapy", is another important strategy. Currently, the key bottleneck to achieve long-term survival for HCC patients is the high postoperative recurrence rate. Postoperative adjuvant therapy, which is aimed at eliminating the intrahepatic microscopic metastases and reducing early relapse, is prevalently adopted in tertiary cancer centers in China. Many published articles also proved that adjuvant therapy could significantly improve survival for HCC patients (5–8).



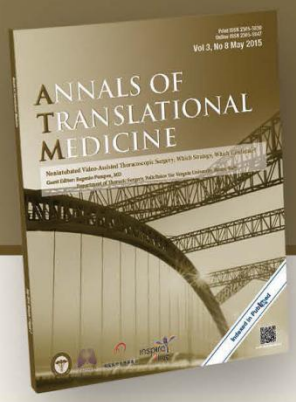
However, the main focus of our study is to explore the effect of BDTT on the long-term prognosis of HCC patients **after liver resection**. **To avoid the influence of different treatment modalities on the prognosis of HCC patients with BDTT**, patients who underwent liver resection alone are selected as the target population in this meta-analysis. **This is the first consideration of our study design**.

Second, we have searched the online databases to identify studies on the topic of HCC/BDTT as comprehensive as possible. **As a result, most of the studies retrieved only compared the survival outcomes between the BDTT and non-BDTT groups under the background/situation of solely surgical interventions**, without reference to other non-surgical treatment. **In our retrieval process, only one study by Shen et al. (9) demonstrated that neoadjuvant TACE significantly reduced the surgical risk of curative liver resection and significantly prolonged median survival in HCC patients with complicating BDTT**. In view of the fact that the lack of studies on (neo)adjuvant therapy for HCC patients with BDTT, we only focused the patients with HCC with BDTT who underwent surgical management. More clinical studies can be designed and conducted in the future to explore the effect of (neo)adjuvant therapy for this special entity of patients.

References:

1. Li C, Wang MD, Lu L, et al. Preoperative transcatheter arterial chemoembolization for surgical resection of huge hepatocellular carcinoma (≥ 10 cm): a multicenter propensity matching analysis. Hepatol Int 2019; 13(6):736-47.
2. Zhang YF, Guo RP, Zou RH, et al. Efficacy and safety of preoperative chemoembolization for resectable hepatocellular carcinoma with portal vein invasion: a prospective comparative study. Eur Radiol 2016; 26(7):2078-88.
3. Li N, Feng S, Xue J, et al. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB 2016; 18(6):549-56.
4. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. J Clin Oncol 2019; 37(24):2141-51.
5. Lee JH, Lee JH, Lim YS, et al. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology 2015; 148(7):1383-91.
6. Wang Z, Ren Z, Chen Y, et al. Adjuvant Transarterial Chemoembolization for HBV-Related Hepatocellular Carcinoma After Resection: A Randomized Controlled Study. Clin Cancer Res 2018; 24(9):2074-81.
7. Zhang XP, Chai ZT, Gao YZ, et al. Postoperative adjuvant sorafenib improves survival outcomes in hepatocellular carcinoma patients with microvascular invasion after R0 liver resection: a propensity score matching analysis. HPB 2019; 21(12):1687-96.
8. Liu S, Guo L, Li H, et al. Postoperative adjuvant trans-arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. Ann Surg Oncol 2018; 25(7):2098-104.

ANNALS OF TRANSLATIONAL MEDICINE



9. Shen Y, Li P, Cui K, et al. Neoadjuvant transcatheter arterial chemoembolization for biliary tumor thrombosis: a retrospective study. Int J Technol Assess Health Care 2016; 32(4):212-17.

AME Publishing Company