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REVIEW

Transarterial Therapy for Hepatocellular Carcinoma Invading the Bile Duct

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Abstract:
Hepatocellular carcinoma invading the bile duct (bile duct tumor thrombus) is an unfavorable condition. Although overall survival following surgical resection among patients with hepatocellular carcinoma with bile duct tumor thrombus is significantly better than that among those treated with transarterial chemoembolization or chemotherapy, surgical resection can be indicated for selected patients. Additionally, systemic therapy is indicated only for patients with Child-Pugh class A. Therefore, transarterial therapy plays an essential role in the treatment of bile duct tumor thrombus. Transarterial chemoembolization with iodized oil and gelatin sponge particles is an established first-line transarterial treatment that can necrotize most bile duct tumor thrombi. However, we should pay attention to symptoms caused by intraductal hemorrhage during transarterial chemoembolization and the sloughing of necrotized bile duct tumor thrombi.

Keywords:
hepatocellular carcinoma, bile duct tumor thrombus, transarterial therapy

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Introduction

Hepatocellular carcinoma (HCC) frequently invades the portal [portal vein tumor thrombus (PVTT)] and hepatic [hepatic vein tumor thrombus (HVTT)] veins, and vascular invasion is one of the negative prognostic factors of HCC [1-4]. It also infrequently invades the bile duct [bile duct tumor thrombus (BDTT)], and the median survival time (MST) of patients with HCC with BDTT treated with best supportive care (BSC) is only 1.6-4.3 months [5]. According to the guidelines for HCC treatment proposed by the Japan Society of Hepatology, surgical resection (SR) is recommended for resectable HCC with vascular invasion, whereas systemic therapy is recommended if it is unresectable. Transarterial therapy, such as transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), is also recommended for patients who are not eligible for SR and systemic therapy [6]. However, vascular invasion generally implies PVTT, and the optimal treatment strategy for HCC with BDTT has yet to be established because of an extremely limited number of articles on treatment outcomes only for BDTT [6]. Therefore, in clinical practice, various approaches, including SR, TACE, HAIC, transarterial radioembolization (TARE), radiotherapy, and systemic therapy, have been employed on the basis of individual patient-tumor conditions, besides endoscopic or percutaneous biliary drainage [7-21].

It has been reported that the overall survival (OS) of patients with HCC with BDTT who underwent SR was significantly better than that of those treated with TACE or chemotherapy [7, 18, 21], although a meta-analysis indicated that the 5-year survival rate of SR in patients with HCC with BDTT was significantly poorer than that of those without BDTT (OR = 0.25; 95% CI, 0.10-0.63; $P = 0.003$), and the OS of patients with HCC with BDTT was reduced by 20 months compared with that of those without BDTT [20]. Liu et al. [21] also reported that the MST in the SR group was 8.0 months longer than that in the TACE group before propensity score matching (PSM) (21.0 vs. 13.0 months, respectively; $P < 0.001$) and 9.0 months longer after PSM (20.0 vs. 11.0 months, respectively; $P < 0.001$). The median disease-free survival (DFS) in the SR group was also 3.5 months longer than that in the TACE group before PSM (7.0 vs. 3.5 months, respectively; $P = 0.007$) and 5 months longer after PSM (7.0 vs. 2.0 months, respectively; $P = 0.007$). However, most patients with HCC with BDTT are

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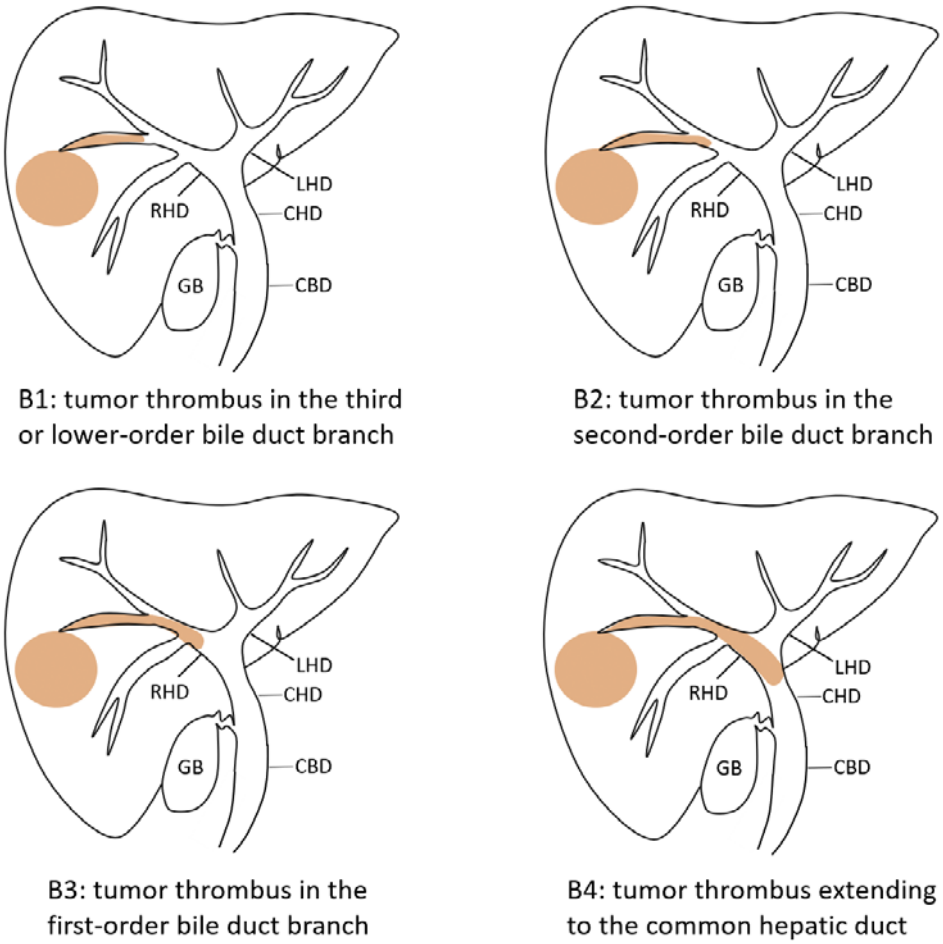

Figure 1. Classification of the degrees of bile duct tumor thrombus (BDTT) proposed by the Liver Cancer Study Group of Japan.
Abbreviations: CBD, common bile duct; CHD, common hepatic duct; GB, gallbladder; LHD, left hepatic duct; RHD, right hepatic duct

not suitable candidates for SR due to advanced tumor stage and poor liver function. In a report by An et al. [18], only 10.9% of patients with HCC with BDTT could be indicated for SR. Systemic therapy, such as immunotherapy and antiangiogenic therapy, has also been developed; however, it is only indicated for patients with HCC with Child-Pugh class A, and its efficacy on BDTT has not been reported [6]. Therefore, in clinical practice, transarterial therapy plays a vital role in the treatment of HCC with BDTT, although it is not recommended by the latest global guidelines [22].

In this paper, the clinicopathological features of HCC with BDTT and indications, techniques, and complications of transarterial therapy are described.

Clinicopathological Features of Hepatocellular Carcinoma with Bile Duct Tumor Thrombus

The prevalence of HCC with BDTT has been documented to range from 0.8% to 9.3% in postmortem and surgical specimens [9, 17, 23, 24]. BDTT represents an intraductal tumor growth resulting from the direct invasion of the infiltrative or mixed (infiltrative and nodular) gross type of HCC [23, 24]. Therefore, it lacks firm adherence to the bile duct wall and can be readily extracted through surgical or endoscopic procedures [9, 25]. The Liver Cancer Study Group of Japan has categorized the degrees of BDTT (B) into five groups: B0 (no tumor thrombus); B1 (a tumor thrombus in the third- or lower-order bile duct branch); B2 (a tumor thrombus in the second-order bile duct branch); B3 (a tumor thrombus in the first-order bile duct); and B4 (a tumor thrombus extending to the common hepatic duct) (**Fig. 1**), and MSTs of SR for B0, B1-3, and B4 HCCs were 5.6, 2.4, and 1.6 years, respectively ($P < 0.0001$) [26]. This study indicates that the degrees of BDTT influence the survival rates of patients even after curative treatment; however, this classification has not been adopted worldwide. BDTT causes obstructive jaundice and cholangitis; therefore, it is clinically termed "icteric hepatoma" [7]. It also causes hemobilia due to the absence of endothelium coverage on the BDTT surface, unlike PVTT and HVTT, and is generally necrotic and hemorrhagic (**Fig. 2**) [24].

Additionally, BDTT is frequently accompanied by PVTT and HVTT (**Fig. 3**) [10, 18, 23, 24], which are the most significant negative prognostic factors for HCC [1-4]. However, the OS of patients with HCC with BDTT is still poor after excluding patients with PVTT and HVTT from the cohort

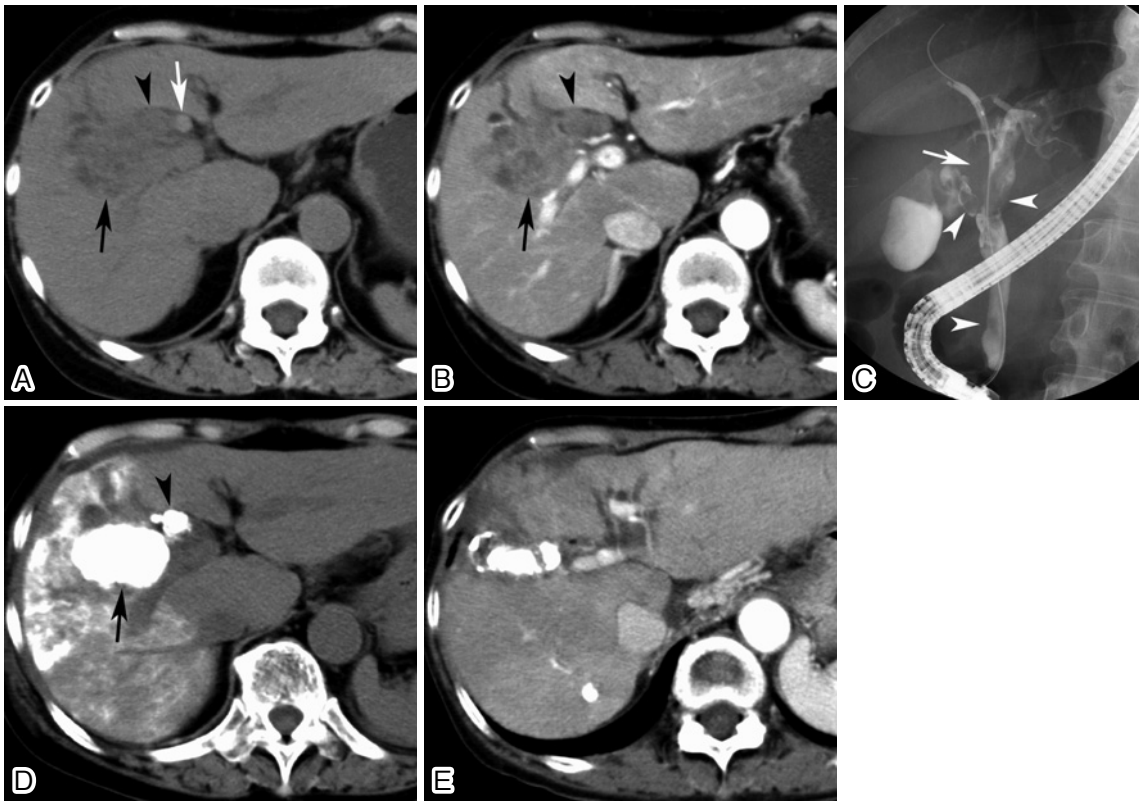

Figure 2. Hemobilia caused by a bile duct tumor thrombus (BDTT).
A. Unenhanced CT showed the tumor (black arrow) invading the bile duct (arrowhead) and hemobilia in the right hepatic duct (white arrow). B. Arterial-phase CT showed the tumor (arrow), BDTT (arrowhead), and increased inhomogeneous enhancement of the liver parenchyma suggesting acute cholangitis. The bile ducts in the anterior segment of the right hepatic lobe were also dilated. C. The serum total bilirubin concentration was 7.4 mg/dL, and endoscopic retrograde cholangiography showed the BDTT extending to the common bile duct (arrow) and coagula (arrowheads). Thereafter, endoscopic nasobiliary drainage (ENBD) was performed (not shown). The serum total bilirubin concentration decreased to 2.9 mg/dL 4 days after ENBD, and two conventional transarterial chemoembolization (cTACE) sessions were performed at 1-month interval (not shown). D. Unenhanced CT performed 1 week after the second cTACE showed a dense iodized oil accumulation in the tumor (arrow) and BDTT (arrowhead), and the serum total bilirubin concentration was normalized 1 month after the second cTACE. However, HCCs and BDTT recurred 6 months after the first cTACE, and cTACE was repeated (ENBD was also performed before cTACE when the serum total bilirubin concentration was ≥3 mg/dL) (not shown). E. Arterial-phase CT performed 3 months after the sixth cTACE (1 year and 6 months after the first cTACE) showed the disappearance of the BDTT, although the bile duct in the lateral segment of the left hepatic lobe was slightly dilated because of the stricture caused by cTACE. The patient died of tumor progression 2 years and 4 months after the first cTACE, despite four additional cTACE sessions.

[18]. A meta-analysis of histopathological studies using surgical specimens revealed several noteworthy findings. First, the BDTT group exhibited a significantly higher proportion of poorly differentiated tumors (OR = 1.88; 95% CI, 1.15-3.05; P = 0.010). Second, HCCs without BDTT demonstrated significantly lower rates of lymphovascular invasion (OR = 4.85; 95% CI, 2.73-8.61; P < 0.001) and portal vein invasion (OR = 5.31; 95% CI, 3.87-7.28; P < 0.001) [19]. These histopathological characteristics may contribute to the unfavorable OS of patients with HCC with BDTT.

Transarterial Therapies for Bile Duct Tumor Thrombus

Indication

It is well known that the serum total bilirubin concentration is one of the significant prognostic factors of patients with HCC treated with TACE, and there is a significant difference in the OS between patients with serum total bilirubin concentrations <3 and ≥3 mg/dL [27]. Hyperbilirubinemia is also recognized as a relative contraindication for TACE due to the substantial risk of postprocedural liver failure [28]; therefore, either endoscopic or percutaneous biliary drainage is generally recommended in cases with a serum total bilirubin concentration ≥3 mg/dL, and additional treat-

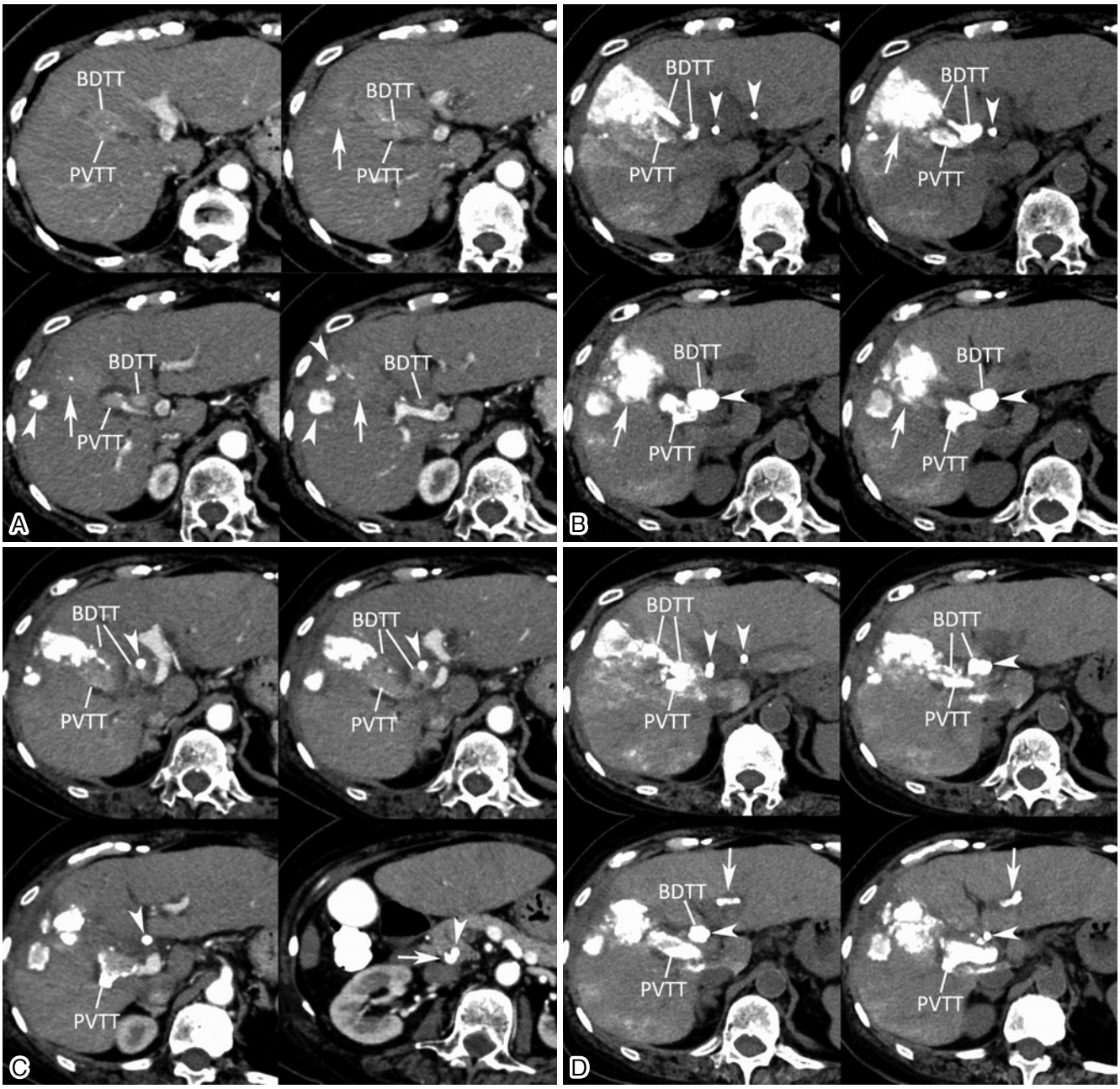

Figure 3. HCC invading the portal vein and bile duct.

A. Arterial-phase CT showed recurrent HCCs 6 years and 10 months after the first conventional transarterial chemoembolization (cTACE) invading the portal vein and bile duct. The arrows indicate a recurrent tumor near the iodized oil accumulated tumor (arrowheads). Endoscopic retrograde cholangiography showed a bile duct tumor thrombus (BDTT) in the right hepatic duct and coagula in the common bile duct. The serum total bilirubin concentration was 8.2 mg/dL, and a plastic stent was placed, bridging between the left hepatic duct and duodenum (not shown). The second cTACE was performed when the serum total bilirubin concentration decreased to 3.6 mg/dL (not shown). B. Unenhanced CT performed 1 week after cTACE showed a dense iodized oil accumulation in the portal vein tumor thrombus (PVTT) and BDTT, as well as in the recurrent tumor (arrows). The arrowheads indicate the plastic stent in the bile duct. C. Arterial-phase CT performed 2 months after the second cTACE showed that some necrotized BDTT tissues dropped in the common bile duct (arrow); however, PVTT and BDTT were still viable. The arrowheads indicate the plastic stent in the bile duct. Therefore, the third cTACE was performed (not shown). D. Unenhanced CT performed 1 week after the third cTACE showed a dense iodized oil accumulation in the PVTT and BDTT. Additionally, some PVTT tissues were detached and migrated into the branch of the left portal vein. However, the patient died of progression of PVTT 6 months after the second cTACE (7 years and 4 months after the first cTACE).

ment for HCC is considered according to the patient-tumor condition following a reduction in the serum total bilirubin concentration [18]. Choi et al. [15] also reported that serum total bilirubin concentration ≥3 mg/dL was a significant predictor of a prolonged hospital stay after TACE (P = 0.023).

In patients with HCC presenting with jaundice caused by a BDTT, Matsumi et al. [29] reported a significantly longer MST in patients who received HCC treatment after endo-

scopic biliary drainage compared with those without treatment (12.0 vs. 2.8 months, respectively; hazard ratio [HR] 4.3; and 95% CI, 4.93-21.5). This indicates that successful drainage can provide patients with HCC with jaundice with an opportunity for extended survival, not only by relief from jaundice but also by the chance to receive additional HCC treatment. Although it is ideal to reduce the serum total bilirubin concentration to <3 mg/dL, the timing of performing additional HCC treatment is controversial, because an abnormal concentration of bilirubin in patients with HCC with BDTT may be independent of liver function and solely reflect the obstruction of bile ducts. Cherqui et al. [8] reported that major SR without preoperative biliary drainage was safe in most patients with obstructive jaundice, and their hepatic synthetic function recovered similarly to that of patients without jaundice. Additionally, the development of interventional therapies has safely paved the way for subsequent antitumor treatment, such as superselective TACE, in patients with obstructive jaundice [19]. In a report by Choi et al. [15] on the outcomes of 53 patients with BDTT treated with conventional TACE (cTACE), 25 (47.2%) patients who had acute cholangitis underwent pre-TACE biliary drainage, and the mean serum total bilirubin concentration was 10.0 ± 6.3 mg/dL at the time of TACE. Conversely, 28 (52.8%) patients who did not have cholangitis underwent TACE without biliary drainage, although eight (15.1%) patients had hyperbilirubinemia (range of the serum total bilirubin concentration, 3.4-21.6 mg/dL). MST and the overall major complication rate were 12.2 months and 13.2%, respectively, but there were no permanent adverse sequelae or deaths within 30 days. This study indicates that controlling cholangitis may be more critical than the actual concentration of total bilirubin. Therefore, the timing of adding active HCC treatment should be decided on the basis of the patient-tumor conditions, referencing the symptoms, such as fever, and the laboratory data including white blood cell counts and the serum c-reactive protein level, rather than relying solely on the serum total bilirubin concentration. Additionally, the placement of a drainage catheter or plastic stent is preferable in cases who are planned for TACE after controlling obstructive jaundice and cholangitis, because metallic stents in the bile duct may cause bile duct complications at high rates after additional TACE sessions [30]. Moreover, it should be well known that biliary intervention is a significant risk factor in developing liver abscess after TACE [31].

Among patients who did not receive active HCC treatment after endoscopic biliary drainage, MST was significantly longer in those with clinical success (at least a 30% reduction of serum total bilirubin concentration) than in those with clinical failure (3.8 vs. 0.73 months, respectively; HR, 2.1; and 95% CI, 2.8-5.7) [29]. This highlights the importance of reducing the serum total bilirubin concentration, even in patients with HCCs that are contraindicated for subsequent therapy. The placement of a plastic stent is usually recommended for patients with obstructive jaundice caused by tumor fragments or blood clots, or with a tumor protruding into the bile duct lumen (**Fig. 2**). The use of an uncovered self-expandable metallic stent (SEMS) for managing obstructive jaundice due to a BDTT is controversial, and Chung et al. [32] reported that OS was significantly extended in patients with HCC undergoing endoscopic biliary drainage with plastic stents compared with those treated with SEMSs (123 vs. 48 days, respectively; $P = 0.005$). Additionally, uncovered SEMSs are typically ineffective in stopping hemobilia (**Fig. 4**). Conversely, a few case reports have demonstrated the usefulness of covered SEMSs for BDTT by achieving direct compression hemostasis at the tumor site [33, 34].

TACE

Although TACE is not actively recommended in patients with HCC with vascular invasion [22], cTACE using iodized oil mixed with chemotherapeutics (doxorubicin, epirubicin, mitomycin C, cisplatin, or miriplatin) and gelatin sponge particles has been performed as the first-line transarterial treatment for unresectable HCC with vascular invasion in a clinical setting [35-38]. However, patients with BDTT frequently have PVTT or HVTT, or both (**Fig. 3**) [10, 18, 23, 24]; therefore, nonselective cTACE carries the risk of severe adverse effects, such as liver failure. In a report by An et al. [18] on the outcomes of 247 patients with BDTT [including 166 (67.2%) patients with both PVTT and BDTT], MSTs for patients who underwent SR, cTACE (including injection of a mixture of iodized oil and chemotherapeutics without gelatin sponge particle embolization for patients with PVTT extending to the main portal vein or Child-Pugh class B liver function), systemic chemotherapy, and BSC were 11.5, 6.0, 2.4, and 1.6 months, respectively ($P = 0.009$ for SR vs. cTACE; $P < 0.001$ for SR vs. systemic chemotherapy; $P < 0.001$ for SR vs. BSC; $P = 0.005$ for TACE vs. systemic chemotherapy; $P < 0.001$ for cTACE vs. BSC; $P = 0.497$ for systemic chemotherapy vs. BSC), and cTACE was found to be a significant prognostic factor on multivariate analysis ($P < 0.001$). As mentioned above, Choi et al. [15] reported more favorable outcomes of cTACE for patients with HCC with BDTT compared with those reported by An et al. [18], and the difference in MST (12.2 vs. 6.0 months) might be caused by different patient-tumor backgrounds in each cohort.

On angiography, the vascular invasion of HCC usually presents with "the thread and streak sign"[38-41], which represents blood spaces and vessels located in and around a tumor cast [39]. BDTT also typically presents the same findings (**Fig. 5** and **6** and Video 1). Although the blood supply of BDTT is not fully understood, it is usually supplied by the same feeder as that of the responsible tumor because it does not attach tightly to the bile duct wall, allowing for a preserved underlying ductal epithelium [23]. However, the tumor vessels reaching a BDTT are relatively small; therefore, selective catheterization into the tumor feeder is essential to perform cTACE for BDTT safely and effectively (**Fig. 5** and **6** and Video 1). Superselective cTACE can necrotize most BDTTs (**Fig. 3** and **5**) [12, 13,

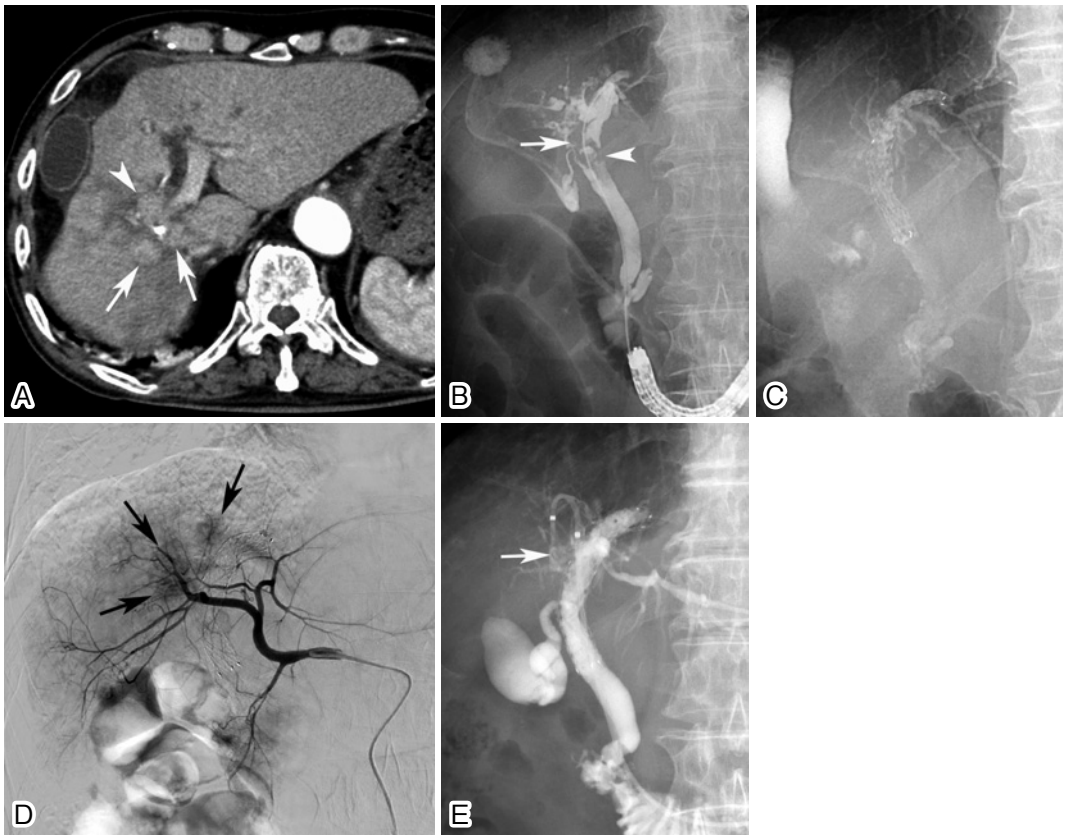

Figure 4. Bland embolization for active hemobilia from a bile duct tumor thrombus (BDTT).
A. The patient had undergone five conventional transarterial chemoembolization (cTACE) sessions for multiple HCCs, and arterial-phase CT performed 4 years and 5 months after the first cTACE showed recurrent tumors (arrows) around the iodized oil accumulated tumor and BDTT in the right hepatic duct (arrowhead). The left hepatic duct was dilated, and increased inhomogeneous enhancement of the liver parenchyma was seen. B. The serum total bilirubin concentration was 4.2 mg/dL, and endoscopic retrograde cholangiography showed BDTT (arrow) and coagula (arrowhead). Then, a plastic stent was endoscopically placed in the bile duct (not shown). C. A self-expandable metallic stent was placed, bridging the BDTT 6 days after plastic stent placement, but the serum total bilirubin concentration was elevated to 7.0 mg/dL due to active hemobilia from BDTT. D. Therefore, bland embolization was planned to stop active hemobilia. A common hepatic arteriogram showed multiple tumors (arrows). Four hepatic arterial branches were embolized with a gelatin sponge slurry approximately 0.5 mm in diameter (not shown). The next day, an endoscopic nasobiliary drainage (ENBD) catheter was placed to monitor the nature of the bile (not shown), and active hemobilia stopped after bland embolization. E. A cholangiogram obtained 1 week after bland embolization through the ENBD catheter showed the disappearance of coagula in the bile duct. The arrow indicates BDTT. The serum total bilirubin concentration decreased to 2.0 mg/dL, and it decreased to 0.9 mg/dL 3 months after bland embolization. Thereafter, the best supportive care was administered, and the patient died of tumor progression 1 year and 5 months after bland embolization (5 years and 11 months after the first cTACE) without clinically problematic cholangitis and active hemobilia.

15, 16]; however, BDTTs frequently recur during the treatment course, necessitating multiple cTACE sessions [14] (**Fig. 2** and **3**). Conversion to SR should be considered in patients with uncontrollable tumors or jaundice, if feasible [15]. cTACE can also be applied to stop active hemobilia, even in selected patients with hyperbilirubinemia [11].

Another application of cTACE for HCC with BDTT is postoperative adjuvant therapy, because 43%-50% of patients with HCC with BDTT show tumor recurrence within the first year following SR [42]. In a report by Chen et al. [42], postoperative adjuvant cTACE (including injection of a mixture of iodized oil and chemotherapeutics without gelatin sponge particle embolization) for the entire remnant liver performed 1 month after SR demonstrated a significant improvement in OS and DFS rates compared with SR alone, even after PSM (for OS, before PSM, $P = 0.026$ and after PSM $P = 0.039$; for DFS, before PSM $P = 0.010$ and after PSM, $P = 0.013$). The outcomes of this study are promising; however, this treatment has not been popularized outside of China.

TACE with drug-eluting beads (DEB-TACE) is also utilized for patients with HCC with vascular invasion; however, the evidence supporting its survival benefit remains insufficient. Although no reports specifically address the therapeu-

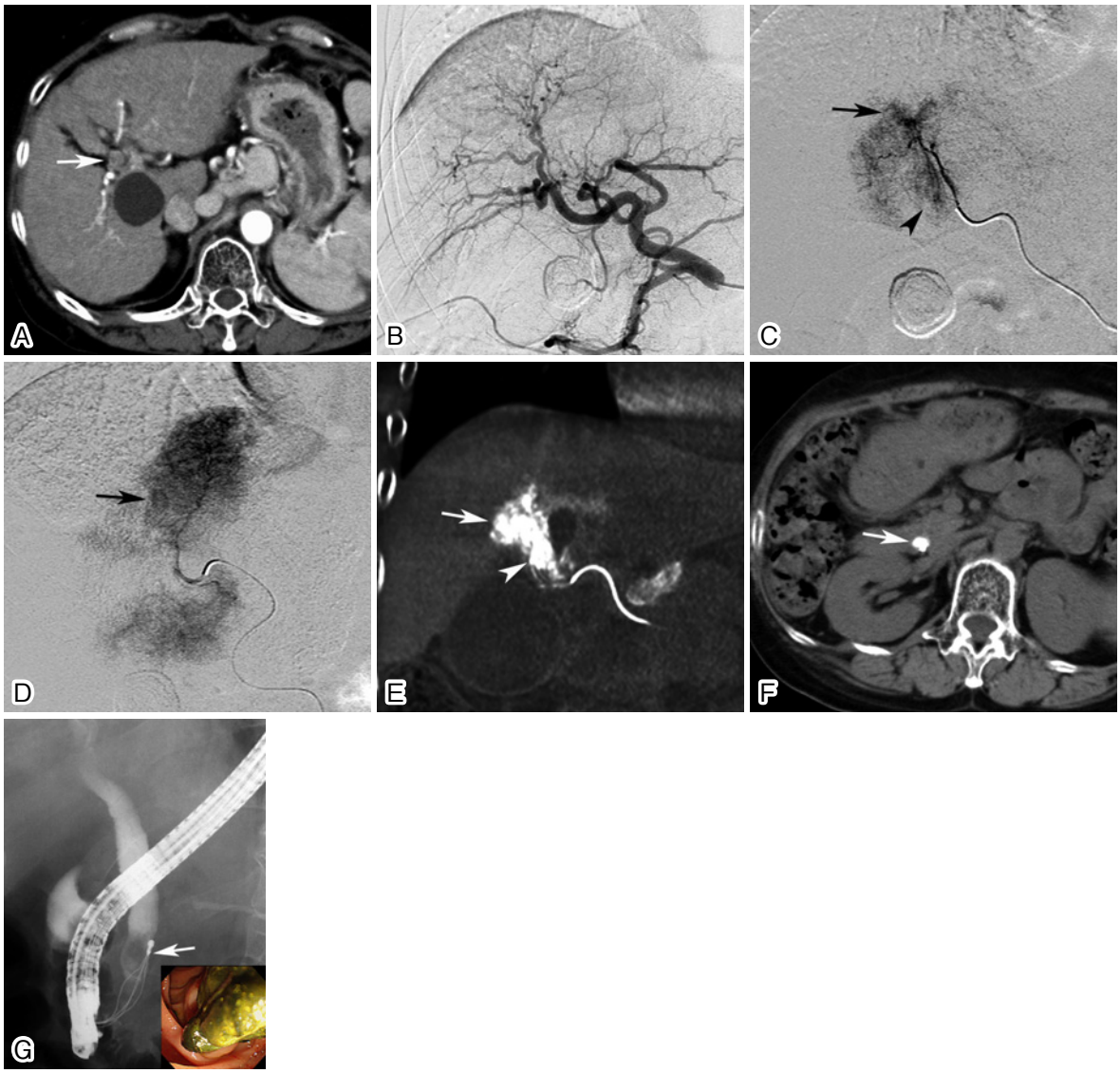

Figure 5. Sloughing of a necrotized bile duct tumor thrombus (BDTT).
A. The patient had undergone two conventional transarterial chemoembolization (cTACE) sessions for HCC, and arterial-phase CT performed 2 years and 4 months after the first cTACE showed a recurrent tumor in segment 4 invading the common bile duct (arrow). The serum total bilirubin concentration was 7.4 mg/dL, but it spontaneously decreased to 3.1 mg/dL 1 month later. B. Therefore, the third cTACE was performed. A common hepatic arteriogram showed no tumor staining. C. An arteriogram of the middle hepatic artery showed the tumor (arrow) and BDTT (arrowhead), and cTACE was performed. D. An arteriogram of the medial subsegmental artery of the left hepatic artery also showed a part of the tumor (arrow), and cTACE was performed. E. A coronal view of cone-beam CT performed immediately after cTACE showed a dense iodized oil accumulation in the tumor (arrow) and BDTT (arrowhead). F. The patient presented with epigastric pain, fever, and jaundice 1 week after the third cTACE, and unenhanced CT showed the dropped BDTT in the common bile duct (arrow). G. Endoscopic retrograde cholangiography showed the dropped BDTT in the common bile duct (arrow), and it was removed endoscopically. However, the tumor in segment 4 recurred, and the patient died of tumor progression 1 year and 4 months after the third cTACE, despite additional cTACE.

tic effects of DEB-TACE on HCC with BDTT, Zhou et al. [43] reported that the objective response rate of DEB-TACE for HCC with PVTT was 79.3% in terms of tumors and 44.8% in PVTT. The median progression-free survival and OS were 5.0 and 9.0 months, respectively, with cumulative OS rates at 6, 12, 18, and 24 months of 72.4%, 41.4%, 22.4%, and 19.0%, respectively.

HAIC

HAIC is primarily performed for HCC beyond the indication of TACE using an indwelling catheter-port system [44, 45], although the evidence supporting the survival benefit has not been proven. Additionally, the definitive indication of HAIC for HCC has yet to be established. Nonetheless, HAIC is one of the treatment options for patients with HCC with vascular invasion, particularly those with both PVTT

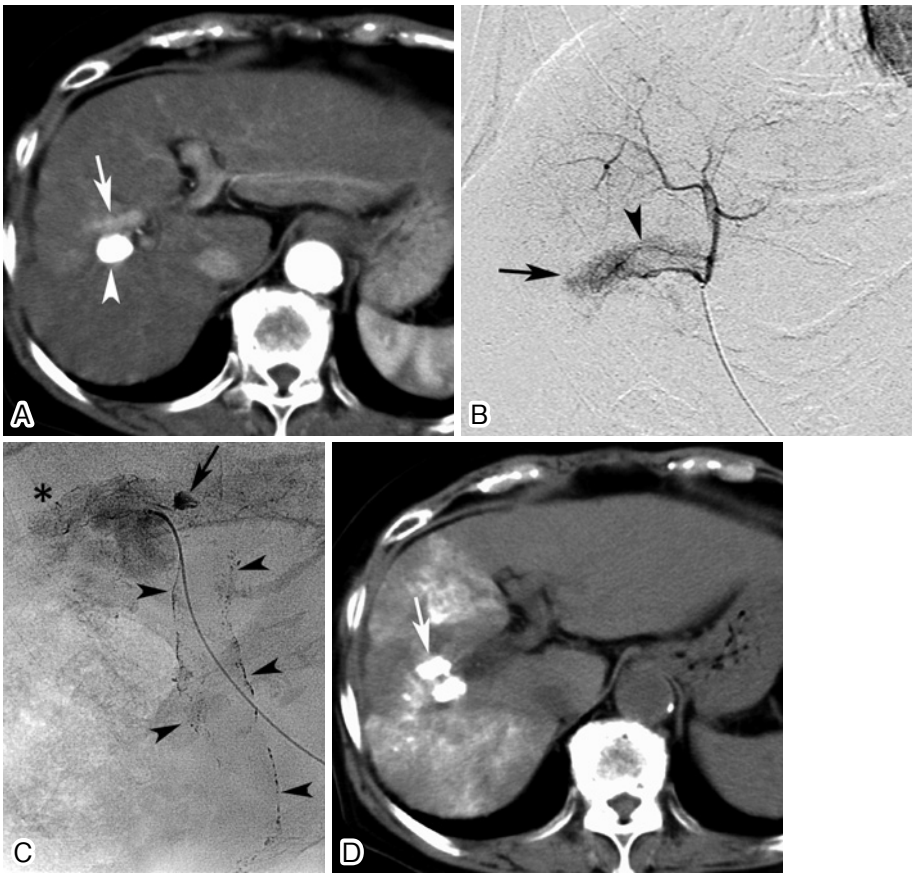

Figure 6. Hemobilia during conventional transarterial chemoembolization (cTACE). A. This patient had undergone 2 cTACE sessions for HCC. Arterial-phase CT performed 1 year and 3 months after the first cTACE showed a bile duct tumor thrombus (BDTT; arrow) near the previously embolized tumor (arrowhead). B. A selective arteriogram of the anterior segmental artery of the right hepatic artery demonstrated BDTT (arrow). The feeder of BDTT arose from the anterior–inferior subsegmental artery of the right hepatic artery and turned left along the direction of tumor invasion into the bile duct (arrowhead). cTACE was performed through this branch. C. During cTACE, iodized oil flowed into the common bile duct (arrowheads) suggesting active hemobilia. Iodized oil was densely accumulated in the BDTT (asterisk), and a vascular lake in the BDTT was noted (arrow). The next day of cTACE, the serum total bilirubin concentration was elevated to 4.1 mg/dL from 2.8 mg/dL. D. Unenhanced CT performed 1 week after cTACE showed a dense iodized oil accumulation in the BDTT (arrow). The serum total bilirubin concentration was decreased to 1.4 mg/dL. Thereafter, four additional cTACE sessions were performed for recurrent HCCs, and the patient was lost to follow-up 4 years and 1 month after the first cTACE due to dementia.

and BDTT (**Fig. 7**). In Japan, a standard regimen for HCC is low-dose cisplatin combined with 5-fluorouracil (low-dose FP), with reported response rates of 48% and MST of 10.2 months for patients with HCC with PVTT [44]. A study by Kodama et al. [45] demonstrated that the response rate and MST in non-TACE refractory patients with HCC with vascular invasion treated with HAIC were significantly better than those treated with sorafenib [39% vs. 0% (P = 0.001), and 13.4 vs. 6 months (P = 0.03)], respectively). Another study reported an 86.3% response rate for a new regimen using fine-powder cisplatin suspended in iodized oil and 5-fluorouracil (new FP) in patients with HCC with PVTT [46].

A one-shot intraarterial cisplatin infusion is also performed for HCC with vascular invasion via a temporarily placed catheter in the hepatic artery [14, 47]. A phase II prospective trial by Ikeda et al. [47] reported a response rate of 28% and an MST of 7.1 months for intraarterial cisplatin infusion in patients with HCC with PVTT. However, apart from a case report in which recurrent BDTT after SR completely disappeared by performing four sessions of a one-shot intraarterial cisplatin infusion [14], there is a lack of cohort studies regarding the therapeutic efficacy of HAIC for HCC with BDTT.

If HAIC is effective and downstaging of the tumor can be achieved, the conversion to more curable treatment options, such as SR, local ablation therapy, or superselective cTACE, should be considered (**Fig. 7**) [44, 46].

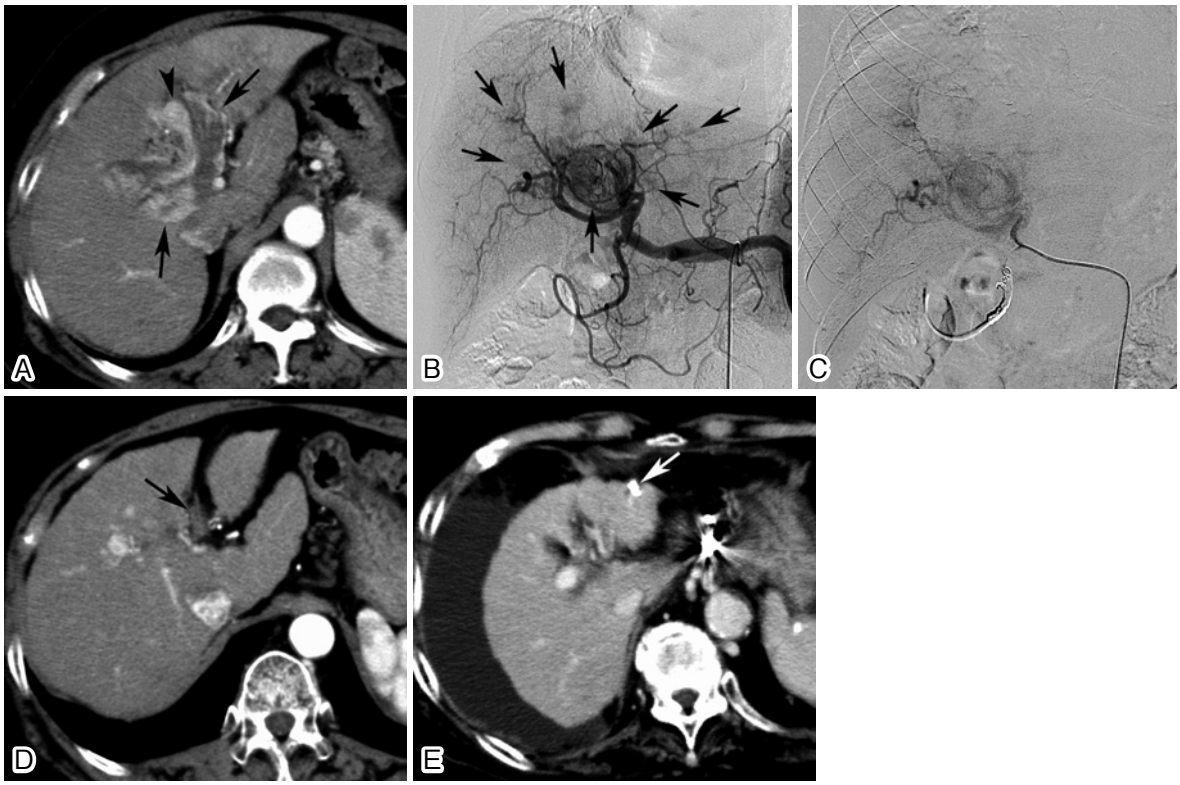

Figure 7. Hepatic arterial infusion chemotherapy (HAIC) for HCC with a portal vein tumor thrombus (PVTT) and a bile duct tumor thrombus (BDTT).
A. Arterial-phase CT showed HCC invading the portal vein (arrow) and bile duct (arrowhead). B. A celiac arteriogram showed the tumors (arrows). C. An indwelling catheter for HAIC was implanted, and two cycles of low-dose cisplatin combined with 5-fluorouracil plus interferon were performed. D. Arterial–phase CT performed 6 months after HAIC showed that all tumors disappeared, although the left portal vein was occluded (arrow) and the left hepatic lobe was decreased in size. However, new tumors developed 1 year and 4 months after HAIC, and seven additional conventional transarterial chemoembolization (cTACE) sessions were performed (not shown). E. Arterial-phase CT performed 7 years after HAIC showed no viable tumors in the liver. However, ascites developed. The arrowhead indicates HCC treated with cTACE. The patient died of liver failure 7 years and 4 months after HAIC.

TARE

TARE using Yttrium-90 (Y-90)-loaded glass or resin microspheres is a novel treatment option for HCC with vascular invasion [48-52], although it has not been approved in several countries, including Japan. The available evidence indicates that TARE is a safe and effective therapy for patients with HCC with major vascular invasion, with MST ranging from 10.7 to 17 months for patients with branch PVTT and 9 to 10.7 months for patients with main trunk PVTT [48]. However, the therapeutic effects of TARE on BDTT have not been reported. A propensity-score-matched and landmark-time-adjusted analyses using the National Cancer Database in the United States demonstrated that TARE was associated with an HR of 0.74 (95% CI, 0.60-0.91; P = 0.005) and an MST of 7.1 months (95% CI, 5.0-10.5) versus 4.9 months (95% CI, 3.9-6.5) for systemically treated patients [50]; however, two randomized controlled trials showed no significant differences in the OS between TARE and sorafenib therapy [51, 52].

In TARE, a selective approach, named "radiation lobectomy/segmentectomy" or "ablative TARE (intended selective delivery of high-dose radiation only to the hepatic segment or lobe)," has emerged as a new technique [50, 53]. It has been reported that ablative TARE was more effective for HCC with PVTT than nonselective TARE, leading to a 2.5-fold increase in OS and a 3.9-fold increase in posttreatment survival [50]. Among the other pretreatment variables, prior DEB-TACE was associated with significantly shorter posttreatment survival and a higher risk of death compared with no prior DEB-TACE [50]. This suggests that it is important to perform selective TARE before DEB-TACE, when TARE is planned for patients with HCC with BDTT. It is considered that the feeders of BDTT are small; therefore, they may be easily attenuated by DEBs. As a result, Y-90-loaded microspheres may be unable to penetrate the feeders of BDTT.

Bland embolization

Bland embolization has less liver toxicity than cTACE and DEB-TACE, because nondrug-loaded microspheres can simply occlude vessels showing mostly non-necrotic vascular changes without hepatic necrosis [54]. Additionally, the necessity of chemotherapeutics in the arterial embolotherapy

of HCC is still controversial and is not supported by high-level evidence [55, 56]. Although the role of bland embolization in the treatment strategy of HCC has yet to be established, it can be a safer option for patients with an advanced age; large or bilobar tumors, or both; or a poor liver function. It can also be performed to stop active hemobilia from BDTT more safely compared with TACE (**Fig. 4**); therefore, its application should not be delayed for patients with hyperbilirubinemia or a poor liver function reserve, or both.

Specific complications of TACE for BDTT

A contrast material pooling within a tumor bed during embolization for HCC is named a vascular lake phenomenon (**Fig. 6** and Video 1) [57]. This indicates the rupture of tumor vessels due to the redistribution of the bloodstream during TACE. Intraductal hemorrhage can also occur during superselective cTACE due to the rupture of a vascular lake caused by the force of injecting embolic agents (**Fig. 6**). When extravasation of iodized oil into the bile duct occurs, embolization with gelatin sponge particles should be performed until the vascular lake disappears.

BDTT is likely to be necrotized by superselective cTACE and readily detaches and drops into the common bile duct when complete tumor necrosis is achieved (**Fig. 3** and **5**). Therefore, it is important to recognize the risk of obstructive jaundice or acute pancreatitis caused by sloughing of a necrotized BDTT [11, 12, 15]. The clinical symptoms and management of detached BDTT are similar to those of choledocholithiasis. For a symptomatic sloughed BDTT, endoscopic removal of the detached BDTT or the placement of a plastic stent is typically required (**Fig. 5**) [11, 12, 15].

Conclusions

BDTT is an unfavorable condition, and the prognosis associated with HCC with BDTT remains poor, despite advancements in various therapeutic modalities. In clinical practice, transarterial therapy, particularly cTACE, plays a vital role in the treatment of unresectable HCC with BDTT, although it is not recommended by the latest guidelines. We should recognize the clinicopathological features of BDTT, perform transarterial treatment safely and effectively according to the patient-tumor conditions, and effectively manage its complications.

Conflict of Interest: The author has received lecture fees from Guerbet.

IRB: This was a review article with no change in patient care, and institutional review board approval is not required at our institution for this type of article. All manuscript preparation processes complied with the Declaration of Helsinki.

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