Optimal liver drainage rate for survival in patients with unresectable malignant hilar biliary obstruction using 3D-image volume analyzer

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Abstract

Background: Drainage exceeding 50% of total liver volume is a beneficial prognostic factor in patients with unresectable malignant hilar biliary obstruction (UMHBO). However, it is unclear what threshold percentage of total liver volume drained ('liver drainage rate') significantly improves survival in patients with UMHBO who received systemic chemotherapy.

Objectives: We aimed to assess the optimal liver drainage rate that improves survival in patients with UMHBO receiving chemotherapy using a three-dimensional (3D)-image volume analyzer.

Design: This study was a single-center retrospective cohort study.

Methods: Data from 90 patients with UMHBO who received chemotherapy after endoscopic biliary drainage using metal stents at Okayama University Hospital from January 2003 to December 2020 were reviewed. The liver drainage rate was calculated by dividing the drained liver volume by the total liver volume using a 3D-image volume analyzer. The primary endpoint was overall survival by liver drainage rate. The secondary endpoints were time to recurrent biliary obstruction (TRBO) and prognostic factors.

Results: The median total liver volume was 1172 (range: 673–2032) mL, and the median liver drainage rate was 83% (range: 50–100). Overall survival was 376 (95% CI: 271–450) days, and patients with >80% drainage ($n = 67$) had significantly longer survival than those with <80% drainage ($n = 23$) (450 days *versus* 224 days, $p = 0.0033$, log-rank test). TRBO was 201 (95% CI: 155–327) days and did not differ significantly by liver drainage rate. Multivariate Cox proportional hazards regression analysis revealed >80% liver drainage [hazard ratio (HR): 0.35, 95% CI: 0.20–0.62, $p = 0.0003$] and hilar cholangiocarcinoma (HR: 0.30, 95% CI: 0.17–0.50, $p < 0.0001$) as significant prognostic factors.

Conclusion: In patients with UMHBO scheduled for chemotherapy, >80% drainage is associated with improved survival. Further prospective multicenter studies are needed to verify the results of this study.

Trail registration: Okayama University Hospital, IRB number: 2108-011.

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Introduction

Endoscopic biliary drainage is often required for obstructive jaundice, followed by chemotherapy for patients with unresectable malignant hilar biliary obstruction (UMHBO) resulting from bile tract, gastric, and other organ malignancies.[1–3] Liver function is a critical factor influencing the use of chemotherapy.[4,5] Vienne *et al.*[6] reported that in patients with UMHBO, drainage >50% of the total liver volume was a predictor of survival. In addition, the Asia-Pacific consensus recommended bilateral or multi-sectoral stenting to achieve drainage ≥50% of the total liver volume and thus, favorable clinical efficacy in patients with high-grade hilar stricture.[7] A recent randomized clinical trial showed that patients with UMHBO undergoing bilateral biliary drainage had better stent patency than those undergoing unilateral drainage.[8] It is considered that larger drainage volumes are obtained with bilateral rather than unilateral drainage, resulting in prolonged patient survival.

Although endoscopic biliary drainage is recommended for patients with UMHBO, the optimal threshold percentage of total liver volume drained ('liver drainage rate') that significantly improves survival has not been clarified. Theoretically, larger volumes of liver drainage should result in greater preservation of residual liver function; this is considered advantageous for continuous chemotherapy and survival.[4,9,10] Thus, the relationship between liver drainage rate and survival should be evaluated, especially for patients with UMHBO receiving chemotherapy.

The Synapse Vincent (Fujifilm Medical Co., Ltd., Minato City, Japan), a three-dimensional (3D)-image volume analyzer for preoperative simulation, demonstrates good efficiency for liver drainage rate analysis, and the system is useful for performing anatomical liver resection.[11] The use of a 3D-image volume analyzer enables accurate determination of liver volumes. Previous studies have reported the relationship between liver drainage rate and survival; however, the liver volumes were not accurately determined. Takahashi *et al.*[12] calculated the summed area volume of each segment *via* manual tracing using computed tomography (CT) with 5-mm slices,[12] and Caillol *et al.*[13] measured the liver drainage rate by dividing the number of drained liver segments by the total number of liver segments. However, the liver volume cannot be accurately determined using these methods.

In this study, we aimed to evaluate the optimal liver drainage rate that contributes to survival in patients with UMHBO receiving chemotherapy using a 3D-image volume analyzer.

Methods

Patients

From January 2003 to December 2020, 127 patients underwent endoscopic biliary drainage with self-expandable metal stents (SEMSs) for UMHBO at Okayama University Hospital. In this study, we included patients aged 20 years or older with obstructive jaundice due to UMHBO. The exclusion criteria were as follows: (1) patients after hepatectomy or gastrectomy with Billroth-II or Roux-en-Y reconstruction, (2) patients who failed scope insertion to the duodenal papilla, (3) patients with Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, or prognosis expected to be less than 1 month due to primary malignant diseases, (4) patients with poorly controlled ascites; and (5) pregnant patients. As shown in Figure 1, 37 patients were excluded for the following reasons: ECOG performance status score of 3 or 4 ($n=25$), lack of contrast-enhanced CT (CE-CT, $n=4$), initial chemotherapy performed elsewhere ($n=4$), declined chemotherapy ($n=3$), and uncontrolled cholangitis ($n=1$). Thus, data from 90 patients receiving chemotherapy after biliary drainage were reviewed retrospectively. All patients were diagnosed with pathology. Patients with primary biliary malignancies were diagnosed through bile duct biopsy, bile juice cytology, or liver biopsy. Other patients were diagnosed based on histology of primary malignancies and radiographic findings such as CT and MRI. We defined intrahepatic cholangiocarcinoma as a mass-forming intrahepatic tumor that invades the hilar bile duct, and hilar cholangiocarcinoma as a tumor predominantly located in the hilar bile ducts and is characterized by bile duct thickening. Gallbladder carcinoma was defined as a tumor predominantly located in the gallbladder that invades the hilar bile duct. Among 90 patients in this study, there were 84 deaths due to primary malignancy.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.
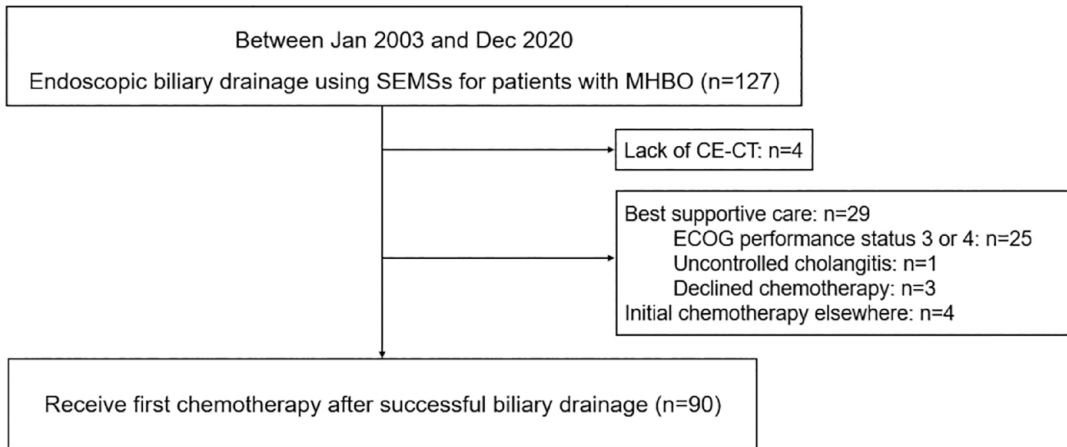
Figure 1. Study flowchart. Ninety patients with UMHBO received chemotherapy after endoscopic biliary drainage using metal stents.
CE-CT, contrast-enhanced computed tomography; ECOG, Eastern Cooperative Oncology Group; SEMS, self-expandable metal stent; UMHBO, unresectable malignant hilar biliary obstruction.

Endoscopic procedures

All patients underwent the procedure *via* a standard endoscopic retrograde cholangiopancreatography (ERCP) technique using a standard duodenoscope (TJF-260, TJF-240, JF-260, or JF-260V; Olympus Optical Co. Ltd., Shinjuku, Japan) under intravenous sedation with meperidine hydrochloride and benzodiazepines. All patients underwent initial endoscopic biliary drainage with plastic stents (PSs), and SEMSs were replaced within 4 weeks after a definitive diagnosis of malignancy. In case of unsuccessful cannulation, we performed percutaneous biliary drainage (PTBD). Subsequently, trans-papillary drainage was finally performed using the PTBD-rendezvous technique. All adverse events were classified according to the ASGE (American Society for Gastrointestinal Endoscopy) consensus guidelines.[14]

In principle, biliary drainage was not performed for any segment without portal vein flow (on CE-CT images) because of the high risk of cholangitis.[6,15] The following SEMSs were used: JOSTENT SelfX units (Abbott Vascular Devices, Redwood City, CA, USA), Zilver Stent (Cook Medical, Winston-Salem, NC, USA), Zeo stent/ Zeo stent V (Zeon Medical Inc., Chiyoda-ku, Japan), Niti-S Biliary Stent (Taewoong Medical Co., Gimpo-si, Korea), and BileRush selective (PIOLAX, Yokohama, Japan). All patients underwent more than two SEMS deployments using the partial stent-in-stent method,[16] and 8-mm or 10-mm diameter SEMSs were used

depending on bile duct diameter. Endoscopic sphincterotomy (EST) was performed to facilitate endoscopic reintervention for recurrent biliary obstruction (RBO), and all SEMSs were placed above the papilla.

Regarding reintervention, after confirming tumor ingrowth/overgrowth, sludge, or hemorrhage as the cause of RBO, 6F or 7F PSs including the TTM (Gadelius Medical, Minato-ku, Japan), Flexima (Boston Scientific, Natick, MA, USA), and Zimmon-type (Cook Endoscopy, Winston-Salem, NC, USA) stents were inserted into the lumen of each previously deployed SEMS. After the first reintervention, PS exchange was performed every 3–4 months.

Liver volumetry

The total and drained liver volumes were measured using the Synapse Vincent. Volumetry of the liver parenchyma, except the portal and hepatic veins, was performed almost automatically based on CE-CT images with the following steps.[11] The liver parenchyma was automatically extracted from consecutive CT images. A 3D image of the whole liver was constructed using a shape recognition algorithm. Next, 3D reconstruction of the portal vein, hepatic vein, and tumor was performed. By setting the start point and direction, the automatic algorithm selected consecutive voxel data with appropriate CT values and branching angles. The stem of the main portal vein was
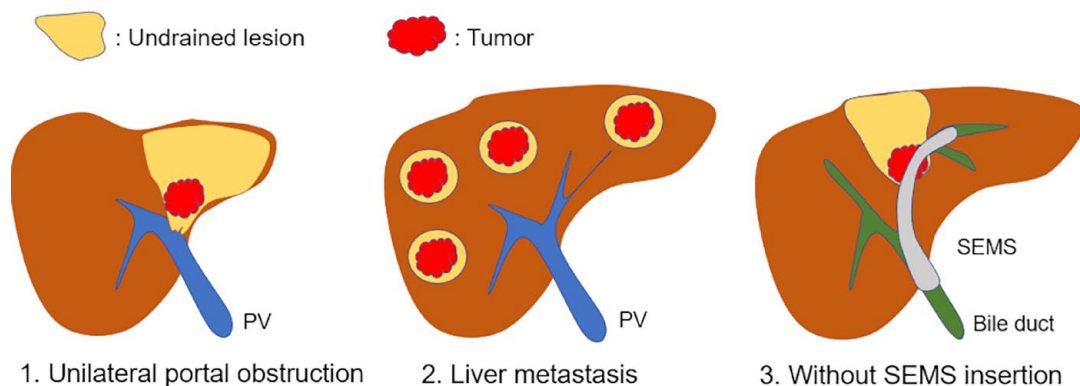
Figure 2. The definition of an undrained lesion on liver volumetry. An undrained lesion was determined for segments without portal blood flow, hepatic metastatic space-occupying lesions, and segments without SEMSs insertion.
PV, portal vein; SEMS, self-expandable metal stent.

set as a starting point and the direction for the peripheral side; the portal tree was then represented automatically. The setting of additional start points was often necessary to extract the thin peripheral branches for complete segmentation. Each hepatic vein was also extracted using the same procedure from the confluence to the inferior vena cava. The tumor was designated on the axial images. At this stage, the extracted portal vein, hepatic veins, and tumors were overlapped, and 3D images were created. The drained lesion was then determined based on ERCP images. By identifying the portal vein perfusing the area drained by metal stents, we calculated the volume of the dominant portal vein territory target. When analyzing the volume of hepatic metastatic or primary tumor lesions, we manually identified and traced lesions occupying the intrahepatic space in CE-CT images. We set the minimum size of hepatic tumor lesions as $5\,mm^2$. Undrained areas included segments without portal blood flow, hepatic metastatic or primary tumor lesions, and segments without SEMS insertion based on ERCP findings. The liver drainage rate was calculated as the ratio of the drained liver volume to the total liver volume (Figures 2 and 3).

Chemotherapy
All patients underwent standard chemotherapy for each primary malignancy after biliary drainage. The chemotherapy regimens were as follows: gemcitabine/cisplatin/S-1 [GCS; $1000\,mg/m^2$ gemcitabine and $25\,mg/m^2$ cisplatin administered on day 1, and S1 (80–120 mg/body) administered

on days 1–7 of a 14-day cycle]; gemcitabine/cisplatin (GC; $1000\,mg/m^2$ gemcitabine and $25\,mg/m^2$ cisplatin administered on days 1 and 8 of a 21-day cycle); gemcitabine (GEM; $1000\,mg/m^2$ gemcitabine alone administered on days 1 and 8 of a 21-day cycle); and S-1 [(80–120 mg/body) administered on days 1–14 of a 21-day cycle]. Patients with malignancies other than cholangiocarcinoma received the following regimens: FOLFOX for colorectal cancer ($400\,mg/m^2$ 5-fluorouracil bolus, $85\,mg/m^2$ oxaliplatin, $400\,mg/m^2$ calcium leucovorin, and $2400\,mg/m^2$ continuous infusion for 46 h administered on day 1 of a 14-day cycle); SOX for gastric cancer [$100\,mg/m^2$ oxaliplatin administered on day 1, and S1 (80–120 mg/body) administered on days 1–14 of a 21-day cycle]; GN for pancreatic cancer ($1000\,mg/m^2$ gemcitabine and $125\,mg/m^2$ nab-paclitaxel administered on days 1, 8, and 21 of a 28-day cycle); EP for neuroendocrine tumor in the gallbladder ($100\,mg/m^2$ etoposide and $20\,mg/m^2$ cisplatin administered on days 1–5 of a 21-day cycle); TC for uterine cervical tumor [$175\,mg/m^2$ paclitaxel and carboplatin (area under the curve, AUC $2\,mg/mL/min$) administered on day 1 of a 21-day cycle]; IFO/EPI for retroperitoneal sarcoma ($1800\,mg/m^2$ ifosfamide and $60\,mg/m^2$ epirubicin administered on days 1–5 of a 21-day cycle); and CDBCA/PEM/ Pembrolizumab for lung cancer [carboplatin (AUC $5\,mg/mL/min$), $500\,mg/m^2$ pemetrexed, and 200 mg/body pembrolizumab administered on day 1 of a 21-day cycle].

Patients meeting the following criteria received chemotherapy: adequate bone marrow (neutrophil
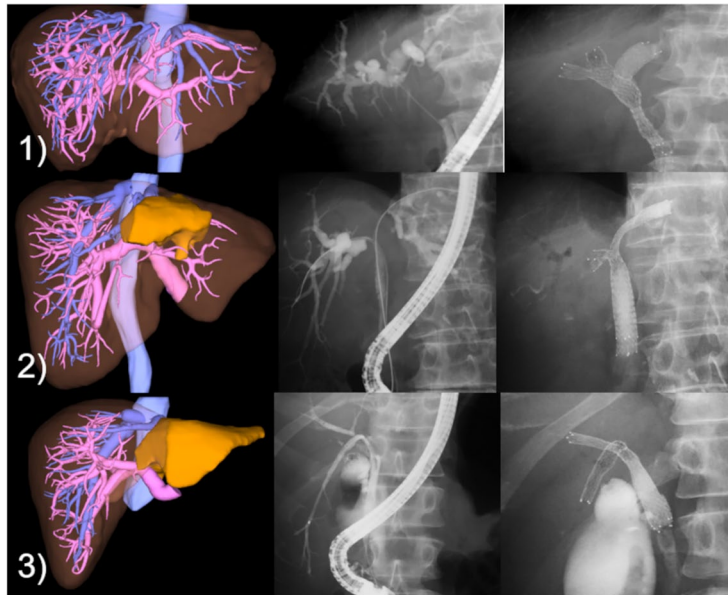
Figure 3. Liver volumetry using a 3D-image volume analyzer.
(1) Complete biliary drainage was performed for Bismuth type II gallbladder cancer. The total liver volume was 863 mL; therefore, the liver drainage rate was 100%. (2) The left medial segment was not drained because of intrahepatic cholangiocarcinoma. The total liver volume was 1072 mL, the drained liver volume was 1022 mL, and the undrained liver volume was 50 mL. Therefore, the drainage rate was calculated as 95%. (3) Biliary drainage was only successful for the right lobe owing to hilar cholangiocarcinoma with left portal obstruction. The total liver volume was 1227 mL, the drained liver volume was 943 mL, and the undrained liver volume was 284 mL. Therefore, the drainage rate was calculated as 77%.

count ≥1500/mm³, platelet count ≥100,000/mm³), liver (total bilirubin ≤3.0 mg/dL, aspartate aminotransferase/alanine aminotransferase ≤150 IU/L), and renal (calculated creatinine clearance using the Cockcroft and Gault formula ≥60 mL/min) function and oral intake. After chemotherapeutic induction, tumor size was evaluated every 3–4 months using CT or magnetic resonance imaging. The antitumor response was assessed using the Response Evaluation Criteria in Solid Tumors from the European Journal of Cancer (version 1.1).

Endpoints

The primary endpoint was overall survival (OS) by liver drainage rates. The secondary endpoints were the time to recurrent biliary obstruction (TRBO), continuous chemotherapy rate after reintervention according to liver drainage rate, and prognostic factors.

OS was defined as the time from a pathological diagnosis of malignancy to death due to any cause or the last visit. The TRBO was calculated from SEMS placement to stent obstruction according to the Tokyo Criteria.[17] Obstruction was diagnosed based on biochemical evidence of cholestasis, that is, elevated liver enzyme levels relative to baseline values along with findings of biliary dilatation on CT or endoscopy. Data regarding patient death without stent obstruction were censored. The clinical success of reintervention was defined as >50% reduction or normalization of serum total bilirubin within 2 weeks after PS placement.

Statistical analysis

Categorical variables are expressed as counts (percentages) and continuous variables as medians (interquartile range). Continuous variables were analyzed using the Wilcoxon or Kruskal–Wallis test and categorical variables using the chi-square or Fisher's exact test. TRBO and OS were determined and compared using Kaplan–Meier estimates and the log-rank test, respectively. Prognostic factors were determined using univariate and multivariate Cox proportional hazards regression analyses. Variables with p-values <0.10 on univariate analysis and with p-values <0.05 on multivariate analysis were considered significant. For statistical analysis, JMP Pro 16 software (SAS Institute Inc., Cary, NC, USA) was used.

Table 1. Characteristics of 90 patients receiving chemotherapy.

Number of patients, *n*	90
Gender, male/female, *n*	50/40
Age, median (range), years	70 (36–88)
Diagnosis, *n*	
Hilar cholangiocarcinoma	56 (62%)
Gallbladder carcinoma	18 (20%)
Intrahepatic cholangiocarcinoma	9 (10%)
Other malignancies	7 (8%)
Unilateral portal obstruction, *n*	15 (17%)
Liver metastasis, *n*	19 (21%)
Bilateral stenting, *n*	70 (78%)
Bismuth type, *n*	
I	3 (3%)
II	11 (13%)
IIIa	10 (11%)
IIIb	4 (4%)
IV	62 (69%)
Number of SEMS, *n*	
2	42 (47%)
3	40 (44%)
4	8 (9%)
Chemotherapy, *n*	
GCS	3 (3%)
GC	28 (31%)
GEM	31 (35%)
S-1	19 (21%)
Others	9 (10%)

GC, gemcitabine/cisplatin; GCS, gemcitabine/cisplatin/S-1; GEM, gemcitabine alone; SEMS, self-expandable metal stent.

Results

Patients characteristics
Patient characteristics are shown in Table 1. The diagnoses were as follows: 56 hilar and 9 intrahepatic cholangiocarcinomas; 18 gallbladder, 2 colorectal, 2 pancreatic, 1 gastric, and 1 cervical carcinoma; and 1 retroperitoneal sarcoma. Bismuth type IV biliary obstruction was present in 62 (69%) patients. Unilateral portal obstruction was noted in 15 (17%) and liver metastasis in 19 (21%) patients. Unilateral drainage was performed in 15 (17%) and bilateral drainage in 70 (78%) patients due to portal obstruction. All cases of unilateral drainage were performed in the right anterior and posterior branches. Patients underwent chemotherapy according to the primary malignancy as follows: GCS ($n=3$); GC ($n=28$); GEM alone ($n=31$); S-1 alone ($n=19$); FOLFOX ($n=2$); EP ($n=2$); SOX ($n=1$); CBDCA/PEM/Pembrolizumab ($n=1$); GN ($n=1$); IFO/EPI ($n=1$); and TC ($n=1$). Eight of 90 (9%) patients underwent metal stent placement with ERCP using a PTBD-rendezvous technique. Adverse events occurred in 9 (10%) patients after SEMS deployment. Five patients had mild pancreatitis. One case each of acute cholecystitis, bile leakage, post-EST hemorrhage, and stent kinking occurred. All patients with pancreatitis showed improvement with conservative treatment. Acute cholecystitis was improved after percutaneous transhepatic gallbladder drainage. Hemostasis for post-EST hemorrhage was achieved by deploying a fully covered SEMS across the papilla. Bile leakage was treated with PTBD, while stent kinking necessitated an additional SEMS deployment.

Volumetry analysis using the Synapse Vincent
The median total liver volume was 1172 mL (range: 673–2032 mL); the median drained volume was 972 mL (range: 512–1707 mL); and the median liver drainage rate was 83% (range: 50–100%). Measured liver drainage rates were 50–69% ($n=10$), 70–79% ($n=13$), 80–89% ($n=31$), and 90–100% ($n=36$). In 19 patients with liver metastasis, the mean rate of involved liver metastasis was 7.04% (range: 0.50–22.9%).

Relationship between TRBO and liver drainage rate
TRBO in all patients was 201 days (95% CI: 155–327). TRBO was 226, 160, and 196 days for drainage rates of 70–79%, 80–89%, and 90–100%, respectively. These values did not significantly differ between the groups (Supplemental Figure 1). TRBO was 189 days (95% CI: 147–314) in patients with >80% drainage and 226 days
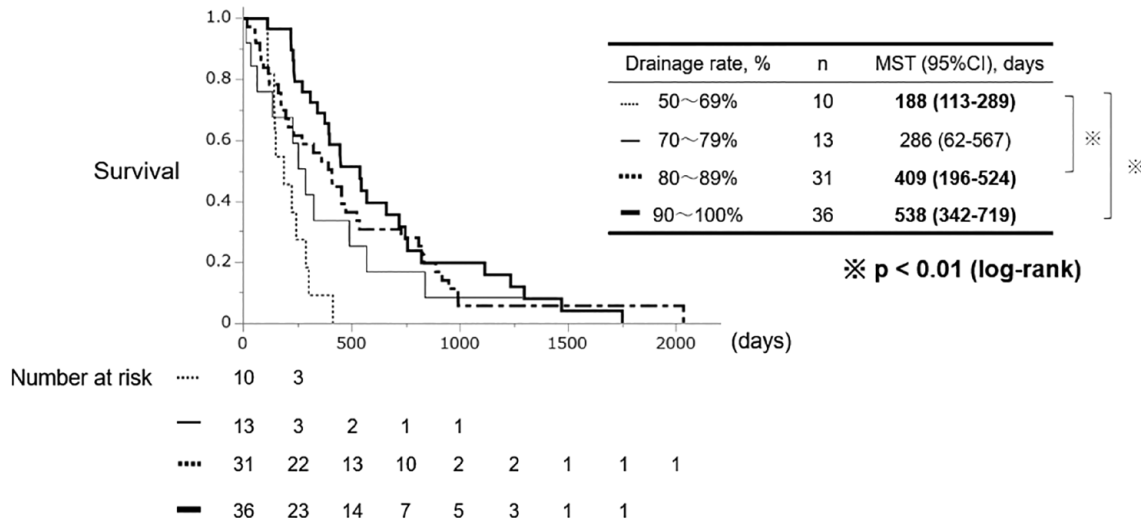
Figure 4. Overall survival by liver drainage rate.
Kaplan–Meier graph shows the overall survival by liver drainage rate. There was a significant difference between patients with 50–69% drainage and those with 80–89% drainage ($p < 0.01$) and 90–100% drainage ($p < 0.01$). MST, median survival time.

(95% CI: 114–unreached days) in those with <80% drainage ($p = 0.809$, log-rank test).

RBO occurred in 56 (62%) patients. The causes of RBO were as follows: tumor ingrowth or overgrowth ($n = 43$), sludge ($n = 12$), and hemobilia ($n = 1$). The causes of RBO did not differ significantly between patients with >80% and those with <80% drainage ($p = 0.698$).

Chemotherapy before RBO
Chemotherapy was continued for 45 patients after reintervention. Best supportive care was given to nine patients with decreasing performance status and to two with reintervention failure (Supplemental Figure 2). The initial chemotherapy regimens were as follows: GCS ($n = 3$), GC ($n = 28$), GEM or S-1 ($n = 50$), and other regimens ($n = 9$). Chemotherapy regimens did not differ significantly between patients with >80% and those with <80% drainage.

Chemotherapy after RBO
Regarding liver drainage rates, 39 of 45 (87%) and 6 of 9 (67%) patients with >80% and <80% drainage, respectively, continued chemotherapy post-reintervention ($p = 0.142$). Of 15 patients with >80% drainage, 8 (53%) were able to continue potent chemotherapy (GCS and GC) after

reintervention (Supplemental Figure 3). By contrast, no patients with <80% drainage were able to continue potent chemotherapy, due to poor liver function (Supplemental Figure 4).

Relationship between OS and liver drainage rate
OS in all patients was 376 days (95% CI: 271–450). The median survival time (MST) was 206 days in the 50–69%, 251 days in the 70–79%, 453 days in the 80–89%, and 446 days in the 90–100% drainage group (Figure 4). Those with >80% drainage had better survival than those with <80% drainage (450 days *versus* 224 days, $p = 0.0033$, log-rank test) (Figure 5).

Analysis of prognostic factors
On univariate Cox proportional hazards regression analysis, hilar cholangiocarcinoma [hazard ratio (HR): 0.36, 95% CI: 0.27–0.57, $p < 0.01$], portal obstruction (HR: 1.65, 95% CI: 0.92–2.96, $p = 0.094$), liver metastasis (HR: 2.50, 95% CI: 1.28–4.22, $p < 0.01$), bilateral stenting (HR: 0.62, 95% CI: 0.37–1.04, $p = 0.068$), and >80% liver drainage (HR: 0.48, 95% CI: 0.29–0.78, $p < 0.01$) were prognostic factors. OS was 473 days (95% CI: 394–728) *versus* 208 days (95% CI: 116–271) in patients with *versus* without hilar cholangiocarcinoma, 303 days (95% CI: 113–409) *versus* 397 days (95% CI: 272–487) in
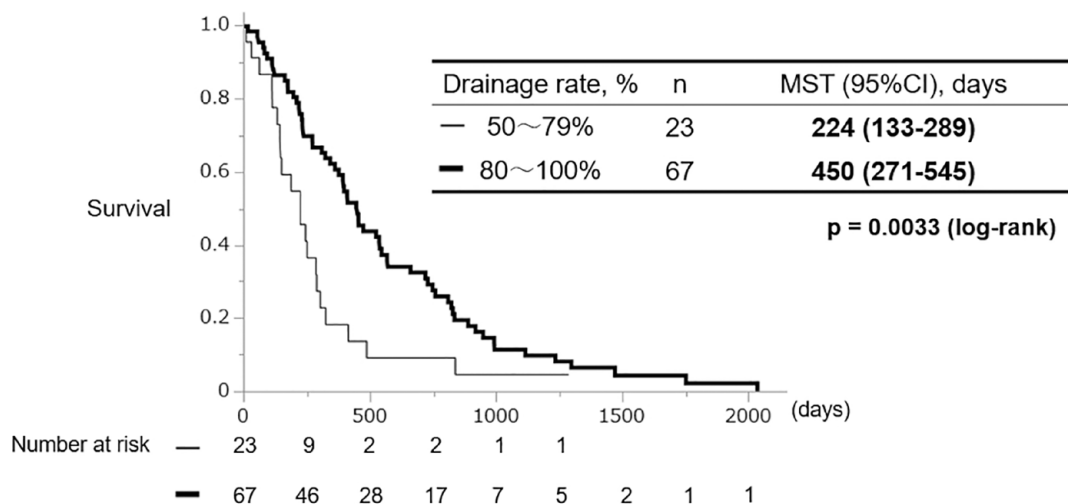
Figure 5. Overall survival in patients with >80% drainage and the others. The Kaplan–Meier graph compared survival in patients with >80% and <80% drainage. Patients with >80% drainage had significantly longer survival.

patients with *versus* without portal obstruction, 121 days (95% CI: 62–286) *versus* 413 days (95% CI: 309–538) in patients with *versus* without liver metastasis, 397 days (95% CI: 272–538) *versus* 244 days (95% CI: 121–409) in patients with bilateral *versus* unilateral stenting, and 450 days (95% CI: 342–545) *versus* 224 days (95% CI: 133–289) in patients with <80% *versus* >80% drainage. On multivariate Cox proportional hazards regression analysis, >80% liver drainage (HR: 0.35, 95% CI: 0.20–0.62, $p = 0.0003$) and hilar cholangiocarcinoma (HR: 0.30, 95% CI: 0.17–0.50, $p < 0.0001$) were significant prognostic factors (Table 2).

Discussion

In this study, we investigated the optimal liver drainage rate in patients with UMHBO receiving chemotherapy using a 3D-image volume analyzer. We found that drainage >80% of the total liver volume contributed to improved OS. To our knowledge, there have been no other reports evaluating the optimal liver drainage rate in patients receiving chemotherapy; this method involves more precise calculation of liver volume than that employed in previous studies.[12,13,18–20]

Vienne *et al.*[6] reviewed 107 patients with UMHBO and reported that those with >50% drainage ($n = 76$) had better survival than those with poorer drainage (119 days *versus* 59 days, $p = 0.01$).

Caillol *et al.*[13] also showed that >80% drainage was a prognostic factor in 65 patients with UMHBO (HR: 2.46, $p = 0.02$).[13] However, these studies did differ from ours, for example, regarding the use of chemotherapy and the accuracy of volumetry measurements. Vienne *et al.*[6] estimated the ratio of three segments (right anterior, right posterior, and left lobe) and calculated the liver drainage rate with relative imprecision. Caillol *et al.*[13] calculated the liver drainage rate by dividing the number of drained liver segments by the total number of liver segments. Thus, the actual liver volume was not measured. A 3D-image volume analyzer can accurately calculate the volume of each segment based on the dominant portal vein flow and exclude segments without portal vein flow. In this study, we defined segments without portal blood flow as undrained areas, and we avoided draining these segments. Hann *et al.*[15] reported that portal obstruction inhibited hepatocyte function in the involved areas and demonstrated a significant correlation between atrophy and portal vein obstruction, with 90% sensitivity, 97% specificity, and 96% positive predictive value ($p < 0.00001$).[15] Moreover, Vienne *et al.*[6] found that drainage of an atrophic segment posed a high risk of cholangitis in patients with UMHBO [odds ratio (OR): 3.04, $p = 0.01$]. Because drainage of the atrophic sector would not improve liver function and increased the risk of cholangitis, we performed biliary drainage for segments with portal vein flow and not for atrophied segments. The

Table 2. Univariate and multivariate analyses of prognostic factors..

Risk factors	Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age ≥75 years	1.08 (0.66–1.80)	0.77		
Male	0.83 (0.54–1.28)	0.41		
Hilar cholangiocarcinoma	0.36 (0.27–0.57)	<0.01	0.30 (0.17–0.50)	<0.0001
Bismuth type IV	1.13 (0.72–1.76)	0.60		
Portal obstruction	1.65 (0.92–2.96)	0.094	1.32 (0.44–3.97)	0.62
Liver metastasis	2.50 (1.28–4.22)	<0.01	1.60 (0.87–2.90)	0.13
Bilateral stenting	0.62 (0.37–1.04)	0.068	0.77 (0.30–1.97)	0.58
Number of SEMS ≥3	0.85 (0.55–1.32)	0.48		
Drainage rate ≥80%	0.48 (0.29–0.78)	<0.01	0.35 (0.20–0.62)	0.0003

CI, confidence interval; HR, hazard ratio; SEMS, self-expandable metal stent.

3D-image volume analyzer is also able to exclude space-occupying lesions from total liver volume measurements by manually tracing the tumor. Thus, we achieved more precise liver volume estimates than those of previous studies.

In this study, the liver drainage rate was not associated with TRBO. A recent randomized controlled study reported non-superiority of bilateral over unilateral biliary drainage *via* SEMS regarding TRBO (11.1 months in uni-SEMS *versus* 4.3 months in bi-SEMS, *p* = 0.11).[21] By contrast, Ashat *et al.*[22] demonstrated that bilateral SEMS stenting yielded a lower reintervention rate than unilateral SEMS stenting on meta-analysis (OR: 0.59, 95% CI: 0.40–0.87, *p* = 0.009). The direct relationship between liver drainage rate and TRBO and the optimal liver drainage rate for achieving prolonged TRBO have not yet been clarified. EST was performed in all cases. Furthermore, all patients received chemotherapy and the regimens in both groups were similar. Thus, we concluded that TRBO was not associated with liver drainage rate.

However, patients with >80% drainage had improved survival in our study. The two groups did not differ significantly regarding the main reasons for discontinuation of chemotherapy including disease progression and decreasing performance status. Chemotherapy continuation rates post-reintervention tended to be higher in patients with >80% *versus* those with <80% drainage (87% *versus* 67%). However, chemotherapy continuation rates may not have differed significantly because of the low number of patients with <80% drainage; this factor may have led to longer survival. Moreover, among 15 patients with >80% drainage receiving potent chemotherapy (GCS or GC), 8 (53%) continued the potent regimen after reintervention. By contrast, no patients with <80% drainage continued the potent chemotherapy regimen, due to poor liver function.

A comparison of liver drainage rates by Bismuth classification showed that the liver drainage rate tended to be lower in cases of severe bile obstruction. However, OS did not differ significantly according to the Bismuth classification (*p* = 0.197, log-rank test) (Supplemental Table 1). Comparing OS in patients with Bismuth III/IV (*n* = 76), patients with liver drainage rates ≥80% had significantly longer OS than patients with rates <80% [524 days (95% CI: 409–728) *versus* 224 days (95% CI: 133–289), *p* = 0.001, log-rank test] (Supplemental Figure 5). This indicates that survival was better in patients with high liver drainage rates, even in cases of severe hilar biliary obstruction. Next, we evaluated the relationship between cholangiocarcinoma and other malignancies in terms of Bismuth classification and

MST. Regarding patients with hilar cholangiocarcinoma ($n = 56$), there was no significant difference in OS by Bismuth classification ($p = 0.0938$, log-rank test). Similarly, for patients with other malignancies ($n = 34$), OS did not differ by Bismuth classification ($p = 0.671$, log-rank test) (Supplemental Table 2). Thus, there was no difference in OS for cholangiocarcinoma compared to other malignancies regarding the type of bile duct obstruction in patients receiving chemotherapy after effective biliary drainage. In this study, various malignancies were included; thus, we also evaluated the survival factors for patients with hilar cholangiocarcinoma ($n = 56$). Results of the multivariate analysis with the Cox hazards model showed that only the drainage rate $\geqslant 80\%$ was a significant prognostic factor (HR: 0.36, 95% CI: 0.17–0.76) (Supplemental Table 3). Drainage rate $\geqslant 80\%$ was a significant prognostic factor for patients with hilar cholangiocarcinoma.

This study has some limitations. First, it was retrospectively conducted with a small sample size. Second, there was population bias. Since the study duration spanned over 17 years, it was difficult to investigate the entire cohort including all patients with UMHBO in our hospital. The strategy for biliary drainage varied according to the treating physician, and no patient had <50% drainage. Third, the deployed SEMSs, malignant etiologies, disease progression, and chemotherapy regimens were not uniform and might have affected TRBO and survival.

In conclusion, drainage >80% of total liver volume was associated with longer survival in patients with UMHBO receiving chemotherapy. An optimal drainage strategy using a 3D-image volume analyzer should be considered before endoscopic biliary drainage. Further prospective multicenter studies are needed to verify the results of this study.

Declarations

Ethics approval and consent to participate
The study was approved by the Institutional Review Board for Human Research (Okayama University Hospital, IRB number: 2108-011; approval date: 26 July 2021) and conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out on the website of Okayama University Hospital.

Consent for publication
Not applicable.

Author contributions
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Taisuke Obata: Data curation; Investigation.

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Shigeru Horiguchi: Data curation; Investigation.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
Not applicable.

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Supplemental material

Supplemental material for this article is available online.

References

1. Kawakami H, Itoi T, Kuwatani M, *et al.* Technical tips and troubleshooting of endoscopic biliary drainage for unresectable malignant hilar biliary obstruction. *J Hepatobiliary Pancreat Sci* 2015; 22: E12–E21.

2. Fukasawa M, Takano S, Shindo H, *et al.* Endoscopic biliary stenting for unresectable malignant hilar obstruction. *Clin J Gastroenterol* 2017; 10: 485–490.

3. Xia MX, Cai XB, Pan YL, *et al.* Optimal stent placement strategy for malignant hilar biliary obstruction: a large multicenter parallel study. *Gastrointest Endosc* 2020; 91: 1117–1128.e9.

4. Eklund JW, Trifilio S and Mulcahy MF. Chemotherapy dosing in the setting of liver dysfunction. *Oncology (Williston Park)* 2005; 19: 1057–1063.

5. Gong J, Cho M and Fakih M. Chemotherapy in patients with hepatobiliary cancers and abnormal hepatic function. *J Gastrointest Oncol* 2017; 8: 314–323.

6. Vienne A, Hobeika E, Gouya H, *et al.* Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. *Gastrointest Endosc* 2010; 72: 728–735.

7. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, *et al.* Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma. *J Gastroenterol Hepatol* 2013; 28: 593–607.

8. Lee TH, Kim TH, Moon JH, *et al.* Bilateral versus unilateral placement of metal stents for inoperable high-grade malignant hilar biliary strictures: a multicenter, prospective, randomized study (with video). *Gastrointest Endosc* 2017; 86: 817–827.

9. Nielson CM, Bylsma LC, Fryzek JP, *et al.* Relative dose intensity of chemotherapy and survival in patients with advanced stage solid tumor cancer: a systematic review and meta-analysis. *Oncologist* 2021; 26: e1609–e1618.

10. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. *J Natl Compr Canc Netw* 2009; 7: 99–108.

11. Takamoto T, Hashimoto T, Ogata S, *et al.* Planning of anatomical liver segmentectomy and subsegmentectomy with 3-dimensional simulation software. *Am J Surg* 2013; 206: 530–538.

12. Takahashi E, Fukasawa M, Sato T, *et al.* Biliary drainage strategy of unresectable malignant hilar strictures by computed tomography volumetry. *World J Gastroenterol* 2015; 21: 4946–4953.

13. Caillol F, Bories E, Zemmour C, *et al.* Palliative endoscopic drainage of malignant stenosis of biliary confluence: efficiency of multiple drainage approach to drain a maximum of liver segments. *United European Gastroenterol J* 2019; 7: 52–59.

14. Cotton PB, Eisen GM, Aabakken L, *et al.* A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010; 71: 446–454.

15. Hann LE, Getrajdman GI, Brown KT, *et al.* Hepatic lobar atrophy: association with ipsilateral portal vein obstruction. *AJR Am J Roentgenol* 1996; 167: 1017–1021.

16. Kawamoto H, Tsutsumi K, Fujii M, *et al.* Endoscopic 3-branched partial stent-in-stent deployment of metallic stents in high-grade malignant hilar biliary stricture (with videos). *Gastrointest Endosc* 2007; 66: 1030–1037.

17. Isayama H, Hamada T, Yasuda I, *et al.* Tokyo criteria 2014 for transpapillary biliary stenting. *Dig Endosc* 2015; 27: 259–264.

18. Mise Y, Tani K, Aoki T, *et al.* Virtual liver resection: computer-assisted operation planning using a three-dimensional liver representation. *J Hepatobiliary Pancreat Sci* 2013; 20: 157–164.

19. Nakayama K, Oshiro Y, Miyamoto R, *et al.* The effect of three-dimensional preoperative simulation on liver surgery. *World J Surg* 2017; 41: 1840–1847.

20. Ohshima S. Volume analyzer Synapse Vincent for liver analysis. *J Hepatobiliary Pancreat Sci* 2014; 21: 235–238.

21. Hakuta R, Kogure H, Nakai Y, *et al.* Unilateral versus bilateral endoscopic nasobiliary drainage and subsequent metal stent placement for unresectable malignant hilar obstruction: a multicenter randomized controlled trial. *J Clin Med* 2021; 10: 206.

22. Ashat M, Arora S, Klair JS, *et al.* Bilateral vs unilateral placement of metal stents for inoperable high-grade hilar biliary strictures: a systemic review and meta-analysis. *World J Gastroenterol* 2019; 25: 5210–5219.

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