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Systematic use of an intraoperative air leak test at the time of major liver resection reduces the rate of postoperative biliary complications

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Abstract

Objective—After hepatectomy, bile leaks remain a major cause of morbidity, cost, and disability. This study was designed to determine if a novel intraoperative Air Leak Test (ALT) would reduce the incidence of post-hepatectomy biliary complications.

Study design—Rates of postoperative biliary complications were compared between 103 patients who underwent ALT and 120 matched patients operated on before ALT was utilized. All study patients underwent major hepatectomy without bile duct resection at 3 high-volume hepatobiliary centers between 2008 and 2012. ALT was performed by placement of a trans-cystic cholangiogram catheter to inject air into the biliary tree while the upper abdomen was filled with saline and the distal common bile duct was manually occluded. Uncontrolled bile ducts were identified by localization of air bubbles at the transection surface and were directly repaired.

Results—The 2 groups were similar in diagnosis, chemotherapy use, tumor number and size, resection extent, surgery duration, and blood loss (all $p > 0.05$). Single or multiple uncontrolled bile ducts were intraoperatively detected and repaired in 62.1% of ALT vs. 8.3% of non-ALT patients ($p < 0.001$). This resulted in a lower rate of postoperative bile leaks in ALT (1.9%) vs. non-ALT patients (10.8%, $p = 0.008$). Independent risk factors for postoperative bile leaks included extended hepatectomy ($p = 0.031$), caudate resection ($p = 0.02$), and not performing ALT ($p = 0.002$) [odds ratio (95% Confidence Interval): 3.8 (1.3–11.8), 4.0 (1.1–14.3), and 11.8 (2.4–58.8), respectively].

Conclusion—ALT is an easily reproducible test that is highly effective for intraoperative detection and repair of open bile ducts, reducing the rate of postoperative bile leaks.

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Keywords

biliary fistula; hepatectomy; complications; outcomes; intraoperative ultrasound

Introduction

Over the past two decades, liver resection has become safer, with mortality rates dropping to less than 5% at major centers.^[1–4] These improvements have come in the setting of progressive expansion of the indications for liver resection and of the use of more aggressive multidisciplinary treatment strategies, including neoadjuvant chemotherapy,^[5, 6] preoperative portal vein embolization (PVE),^[7, 8] extended hepatectomy,^[9] repeat resections,^[10] two-stage hepatectomy and the reverse approach.^[2, 4, 11–15]

Advances in surgical technique and better understanding of liver anatomy and physiology have facilitated a decrease in postoperative hepatic insufficiency rates and in perioperative blood transfusion needs. However, these improvements have not been paralleled by a decrease in the rate of postoperative bile leak, which remains the Achilles' heel of liver resection.^[2, 4, 11–15] In fact, in a recent study examining a large experience with liver resection performed at our institution, we found progressively increasing rates of postoperative bile leaks over 15 years. These data suggest that, as the complexity of liver resections has increased, postoperative bile leak has become one of the most important problems in liver surgery.^[15]

While in many cases a postoperative bile leak can be managed successfully with drainage and antibiotics,^[16] it almost always entails longer length of stay and increased hospital costs. Furthermore, in some cases, post-hepatectomy bile leak can lead to a cascade of systemic morbidity stemming from intra-abdominal sepsis. Documented secondary complications associated with bile leak include venous thromboembolism, further invasive procedures including re-laparotomy, and increased risk of mortality.^[17–19]

Currently, there is no standard method for the prevention of postoperative bile leak. To address this issue, the following study was designed to determine if systematic utilization of a refined intraoperative "Air Leak Test" (ALT) could: 1) improve the detection and repair of intraoperative open bile ducts, and 2) reduce the rate of postoperative bile leak.

Material and Methods

Patients

The study population included 223 consecutive patients undergoing a major liver resection (> 3 segments), without biliary-enteric anastomosis, at the following 3 tertiary hepatobiliary centers: The University of Texas MD Anderson Cancer Center (MDACC), Houston, Texas, USA; Ospedale Mauriziano Umberto I, Torino, Italy; and University Hospital Agostino Gemelli, Rome, Italy. All liver resections were performed by five experienced liver surgeons (JNV, TA, LC, GN, FG).

For data analysis, study patients were divided in two groups. The primary study group included 103 patients with an intraoperatively accessible cystic duct who underwent the ALT starting in May 2009. This group includes all initial cases at each center where the technique was used without filtering any "learning curve" cases from the data collection. The second group included 120 patients, proportionally drawn from all centers, who were operated upon during the immediately preceding time period (January 2008 – May 2009) before the use of ALT and those patients treated in the time period overlapping the

introduction of the ALT in cases where ALT could not be performed because of inaccessibility of the cystic duct due to prior cholecystectomy. This study was approved by institutional review boards of all participating centers.

Preoperative Assessment

The pre-operative assessment included a high-resolution computed tomography using liver protocol (rapid injection of 3–5 mL/sec of intravenous contrast, three phases, and 2.5- to 5-mm slice thickness through the liver) and/or magnetic resonance imaging using liver protocol and contrast agents. The future liver remnant volume was calculated as previously described.^[20] If the calculated standardized future liver remnant volume was inadequate, preoperative PVE was performed.^[21]

Surgery

Intraoperative ultrasonography with a 5- to 7.5-MHz probe (Aloka Co. Ltd., Tokyo, Japan) was routinely performed to confirm the findings from preoperative imaging, to exclude previously undetected lesions, to visualize the anatomic relationships between the tumor and vascular and biliary structures, and to delineate the proper transection plane.

Extent of hepatectomy was defined according to Brisbane 2000 terminology.^[22] The parenchymal transection technique was chosen by the surgeon on the basis of tumor size, anticipated extent of resection, and liver parenchyma condition. At MDACC, the “two-surgeon technique”, using a combination of an ultrasonic dissector (primary surgeon) and a saline-linked cautery (second surgeon), was used in most cases.^[23] At Ospedale Mauriziano and Ospedale Gemelli, liver resections were performed using a similar technique with ultrasonic dissector, together with bipolar forceps with continuous irrigation and absorbable clips or suture ligation for minor and larger vessels or bile ducts, respectively.

A total or selective hepatic inflow occlusion (Pringle Maneuver) was used in the majority of cases at MDACC for periods of up to 15 minutes alternating with 5 minutes of restored inflow. At Ospedale Mauriziano and Ospedale Gemelli, Pringle Maneuver was used only when persistent or major bleeding occurred. In both groups, an initial evaluation of the transection surface was made to detect open bile ducts by direct visualization and by evaluation with a white gauze compress with closure by placement of polypropylene sutures.

Air Leak Test

In the ALT cohort (e.g. patients without previous cholecystectomy), at the end of the parenchymal transection and after obtaining hemostasis and closing every evident bile leak detected by white gauze on the transection surface, a disposable cholangiography catheter was inserted into the cystic duct and secured with a silk tie. The ALT was performed in two steps consisting of the injection of air to fill the biliary tree while occluding the distal common bile duct by finger compression.

During the first step of the ALT, a liver ultrasound over the remaining liver parenchyma was performed while air was injected (Figure 1A). The ultrasonographic visualization of pneumobilia documented bile duct patency (Figure 1B). Nonvisualization of pneumobilia was suggestive of a bile duct obstruction, a massive air leak via a large open bile duct, or (most commonly) incomplete manual occlusion of the distal common bile duct. This first step was previously described as a means to intraoperatively detect bile duct stricture.^[24] The second step of the ALT consisted of filling the right upper quadrant of the abdomen with sterile water or saline, submerging the liver transection surface. With repeat trans cystic air injection, the appearance of air bubbles on the water surface indicated the presence of one or more open bile ducts (Figure 2A). Each leaking bile duct was identified by gradually

suctioning the pooled sterile water or saline and directly repaired with polypropylene suture (Figure 2B). This portion of the ALT was repeated as needed until there no further air leaks were detected.

Postoperative Outcomes, Data Collection, and Definitions

Complications were graded as previously described.^[25] Grade I–II complications were defined as minor complications, and grade III or greater were categorized as major complications. Hospital stay was measured from the day of operation to the day of discharge or death. Postoperative mortality included deaths within 90 postoperative days.

Placement of perihepatic drains at the time of surgery was at the discretion of the operative team. If utilized, abdominal drains were removed before hospital discharge if the output was non-bilious and non-purulent. Bile leak was defined as a drain fluid bilirubin concentration at least three times the serum bilirubin concentration on or after postoperative day 3. This was analyzed only when the drain fluid character was suspicious for bile leak, when there was a need for radiologic or operative intervention for abdominal fluid collections, and/or when there was peritonitis that suggested a clinically significant bile leak. Bile leaks were classified according to the definition of the International Study Group of Liver Surgery.^[26] Grade A required little or no change in clinical management. Grade B required a change in clinical management (e.g. additional diagnostic or interventional procedures) but remained manageable without re-laparotomy. It included Grade A bile leaks lasting for >1 week. Grade C required relaparotomy. As previously described, perihepatic abscess, hemorrhage, postoperative hepatic insufficiency and bile leaks were classified as liver-related complications.^[15, 27]

Statistical Analysis

Statistical analysis was performed with SPSS (version 19.0; SPSS Inc., Chicago, IL). Continuous data were expressed as medians (range) or frequency (percentage) and compared with the Mann-Whitney U test. Categorical data were compared by the chi-square or Fisher exact test as appropriate. Perioperative variables significantly associated with postoperative bile leak (overall and Grade B and C) on univariate analysis were entered into a multivariate logistic regression analysis in a backward stepwise manner. $P < 0.05$ was considered statistically significant in all analyses. A power calculation determined that the number of patients in each group provided the ability to detect a 9% difference in the rate of postoperative bile leak with an alpha error level of 0.05 and a beta error level of 0.12.

Results

Overall perioperative and postoperative characteristics

In the combined ALT and non-ALT group, the median age was 55.7 years (range 12 – 84), 121 patients (54.3%) were male, and 177 patients (79.4%) had an American Society of Anesthesiologists (ASA) score 3. Main indications for liver resections were colorectal liver metastases in 127 patients (57%), hepatocellular carcinoma in 30 patients (13.4%), biliary tumors in 22 patients (9.8%), neuroendocrine metastases in 19 patients (8.5%), benign tumors in 5 patients (2.2%), and other malignancies in 20 patients (9.1%). A preoperative PVE was performed in 81 patients (36.3%). An anatomic resection was performed in 160 patients (71.8%), with an extended hepatectomy in 102 patients (45.7%) and one or more additional liver-related procedures in 111 patients (49.7%).

During intraoperative examination, at least one bile leak was identified and repaired in 74 (33.2%) cases. Overall and major postoperative complication rates were 43.5% and 15.7%, respectively. Postoperative death occurred in 3 patients (1.3%). Causes of death included

liver failure (n=1), cardiac arrest with subsequent multi-organ failure (n=1), and infected biloma complicated by hepatorenal syndrome in (n=1).

Comparison of the ALT and Control group

Clinicopathological characteristics did not differ significantly between ALT and non-ALT patients (Table 1). Specifically, the two groups were similar in terms of age, gender, ASA score, rate of previous PVE, diagnosis, characteristics of underlying liver parenchyma, number and size of tumors (all $p>0.05$). Comparing operative characteristics, there were no differences between study groups except for a 7-times higher rate of intraoperative air leak detection/repair in the ALT group (62.1% of ALT patients vs. 8.3% of non-ALT patients, $p<0.001$) (Table 2). Postoperatively, less biliary complications occurred in the ALT group (1.9% vs. 10.8% in the non-ALT group, $p=0.008$). The difference in more severe (Grade B–C) bile leaks was also significant between the 2 groups (7.5% in non-ALT vs. 1% in ALT, $p=0.022$). In addition, among patients with postoperative bile leaks, a shorter median length of stay was observed in the ALT group (6 vs. 21 days, $p=0.027$) (Table 3).

Risk factors for overall and Grade B–C bile leaks

In univariate analysis, risk factors associated with a higher risk of both overall and grade B–C postoperative biliary complications included preoperative PVE ($p=0.048$ and 0.039 , respectively) and caudate lobe resection ($p=0.041$ and 0.035). Extended hepatectomy was associated with grade B–C postoperative bile leak ($p=0.046$), but not with overall bile leak ($p=0.092$). Use of the ALT was associated with a lower risk of both overall and grade B–C postoperative bile leak ($p=0.008$ and 0.022) (Table 4). In multivariate analysis, extended hepatectomy, caudate resection, and not performing the ALT were independently associated with a higher risk of both overall ($p=0.021$, odds ratio, OR[95% confidence interval, CI]: 3.806[1.229–11.790]; $p=0.03$, OR[CI]: 4.046 [1.142–14.334]; and $p=0.002$, OR [CI]: 11.76 [2.40– 58.82], respectively) and grade B–C bile leak ($p=0.029$, OR [CI]: 6.203 [1.209–31.816]; $p=0.013$, OR [CI]: 6.702 [1.490–30.146]; and $p=0.012$, OR [CI]: 16.66 [1.83–142.85], respectively) (Table 5).

Discussion

Postoperative biliary complications remain a major problem in liver surgery. Multiple strategies have been used to reduce the rate of this complication. However, as the overall magnitude of liver surgery has increased due to improved mortality rates, there has been little improvement in the rate of postoperative bile leak.^[2, 4, 11–15] In the current study, use of the ALT improved the detection of open bile ducts not readily visualized on the transection surface, and allowed for the intraoperative repair of these covert biliary fistulas. Most importantly, systematic utilization of the ALT was associated with a significant decrease in the incidence and severity of postoperative biliary complications. In multivariate analysis, the most important independent modifiable risk factor for patients suffering a post-hepatectomy bile leak was not undergoing the ALT. As such, the ALT is an important advance which provides surgeons with a reliable, reproducible, and low-cost technique to lower the rate and clinical sequelae of bile leaks after hepatectomy.

In a recent study, we reported an increase in bile leaks over time paralleling an increase in the complexity of hepatectomy (3.7% before 2006 vs. 5.9% after 2006, $p=0.011$).^[15] This difference in bile leak rate persisted after excluding patients who underwent a biliary-enteric anastomosis and was even greater when considering only patients undergoing major hepatectomy (4.7% vs. 9.2%, $p=0.005$). Given this increasing frequency of postoperative biliary complications, there existed a clinical imperative to focus the current study on patients undergoing major hepatectomy. These patients have a higher risk of postoperative

bile leak and would derive the most benefit from the intraoperative detection of open bile ducts.

During the past decade, several bile leak tests have been proposed, with none gaining wide acceptance. The intraductal injection of saline is a low-cost and reproducible technique, but the transparent solution makes this technique inadequate for detecting small ducts.^[28] The injection of dye solutions (e.g. methylene blue and indocyanine green) has been recommended.^[13, 18, 29, 30] However, these solutions need to be dense in order to allow the visualization of the leak site. The related disadvantages of this approach include the following: 1) the indelible coloration of the transection surface, which can mask additional small open ducts, 2) the impossibility to wash out the staining and, consequently, 3) potential reduced sensitivity for the detection of leak with repeated tests. Some centers have reported the saturation of the cut surface of the liver with hydrogen peroxide to detect bile leaks,^[31] however this practice comes with a potential risk of expansion air embolism via open hepatic veins.

Standard cholangiography with radiographic contrast is the gold standard test for intraoperative detection of open bile ducts, but it is time-consuming and exposes patients and medical staff to radiation. The “White Test,” based on the intraductal injection of 5% fat emulsion, has been reported to be feasible, sensitive, low-cost, and repeatable.^[32] However, the study reporting on this technique was diluted by the inclusion of 29 patients (21% of the total cohort) undergoing bile duct resection and biliary-enteric anastomosis.^[33] Furthermore, the fat emulsion is a foreign body and its intraductal injection can be associated with adverse effects such as allergic reactions, fat emboli, immunosuppressive effects, and fungal infections. The only technique supported by a randomized clinical trial is based on the transductal injection of indocyanine green while performing a fluorescent cholangiography using an infrared camera.^[34] This test requires extended time, specialized equipment and complex algorithms that indirectly identify open bile ducts on a monitor while performing the test with the operating room lights off. Combined, each of these approaches poses significant obstacles to wide-spread utilization.

In contrast, by utilizing common, inexpensive and familiar elements, the ALT overcomes many of these disadvantages. It requires no additional technology. It is not associated with staining of the surgical field, thus allowing repeat testing as needed. Finally, because it only requires air injection, it does not expose patients to the risks associated with other techniques. After a short learning curve, the total time for the procedure was less than 30 minutes. As an additional advantage, the completion of the ALT and the finding of no residual open bile ducts have encouraged the surgeons in the study to decrease their reliance on prophylactic drain placement, potentially improving patient satisfaction and reducing drain-associated complications.

The validity of our results is supported by (1) the multicenter design of the study; (2) complete reporting of the initial experience with the technique at each center without filtering any “learning-curve” cases from the data, providing support for the generalizability of the test and of its results; (3) the study patient number, which is the highest among previously published series examining novel techniques for bile leak prevention; (4) the associated statistical power indicating that detection of a 9% reduction in the bile leak rate was statistically significant, and (5) the clinically relevant decrease in postoperative bile leak rate (from 11% in the non-ALT to 2% in the ALT group). Based on these safety and efficacy results, we suggest that this approach be more widely adopted, tested, and confirmed.

There are some anatomic limitations of the ALT. Obviously, patients who have previously undergone cholecystectomy present an obstacle to the ALT. In these cases, identification

and cannulation of the remnant cystic duct for ALT can be considered. A second option is to cannulate the common bile duct or common hepatic duct with a small bore needle for the ALT with primary repair of the choledochotomy. A second limitation is in patients with anatomic variations including a low cystic duct confluence with the common bile duct. This anatomic variation may prevent the air from reaching the proximal bile ducts as the occlusion of the distal common bile duct by finger compression will be at or above the cystic duct confluence. However, this anatomic variation will not lead to a false-negative ALT because it will be recognized in the first part of the ALT as an inability to produce ultrasound-detectable pneumobilia within the hepatic parenchyma. A final clinical 'pearl' regarding the technique is that all diagnostic ultrasonography of the liver parenchyma, including Doppler examination of intrahepatic vessels following resection, must be completed prior to performing the ALT as the presence of diffuse air in the bile ducts limits the visualization of other intrahepatic structures for a short time after the ALT.

In conclusion, the ALT is a novel intraoperative test which is both simple to execute and reproducible across institutions. It adds minimal time and cost to the operation, is not associated with morbidity, and has demonstrated clear efficacy. The early success with the ALT has made it a routine part of major hepatectomy at the study institutions. By utilizing the ALT to reduce bile leak-related morbidity and mortality, hepatobiliary surgeons have the opportunity to further improve the postoperative outcomes of their patients.

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Figure 1.

Liver ultrasonography during transcystic air injection while the distal common bile duct is occluded by finger compression (A). Ultrasonographic visualization of diffuse acoustic shadowing indicates pneumobilia and thus documents bile duct patency (B).

Figure 2.

Air bubbles along the right hepatic duct stump during transcystic air injection (A, white arrows) indicate the presence of an open bile duct. Water is then slowly removed in order to precisely locate the open duct. The leaking duct is repaired with a non-absorbable polypropylene suture (B, white arrow), and the ALT is repeated to confirm effective repair.

Table 1

Comparison of clinical and pathological characteristics in the Air Leak Test vs. non-Air Leak Test group.

<i>Clinical features</i>	Non-Air Leak Test group (n=120) n (%)	Air Leak Test group (n=103) n (%)	<i>p</i>
Median Age (range)	57 (12 – 84)	55 (13 – 77)	0.212
Sex male	60 (50)	61 (59.2)	0.168
ASA score >2	84 (81.6)	93 (97.5)	0.456
Previous PVE	44 (36.7)	37 (35.9)	0.908
Diagnosis			
Hepatocellular carcinoma	17 (14.2)	13 (12.6)	0.193
Colorectal metastases	61 (54.8)	66 (64.1)	
Biliary tumors	14 (11.7)	8 (7.8)	
Other malignancies	12 (10)	8 (7.8)	
Benign	5 (4.2)	0	
NET metastases	11 (9.2)	8 (7.8)	
<i>Pathologic features</i>			
Non-tumor parenchyma			
Portal fibrosis	12 (10)	5 (4.9)	0.149
Steatosis >30%	13 (10.8)	11 (10.7)	0.971
Portal inflammation	19 (15.8)	23 (22.8)	0.216
Median number of tumors (range)	2 (1 – 16)	2 (1 – 21)	0.168
Median diameter (range), mm	35.5 (6 – 250)	38 (4 – 220)	0.811

Data are expressed as absolute numbers (percentage) or medians (range).

Abbreviations: ASA, American Society of Anesthesiologists; PVE, Portal Vein Embolization; NET, neuroendocrine tumor.

Table 2

Comparison of intraoperative characteristics in the Air Leak Test group vs. non-Air Leak Test group.

<i>Operative features</i>	Non-Air Leak Test group (n=120) n (%)	Air Leak Test group (n=103) n (%)	<i>P</i>
Anatomic resection	92 (76.7)	68 (66)	0.078
Extended hepatectomy	48 (40)	54 (52.4)	0.063
Caudate resection	12 (10)	19 (18.4)	0.069
Associated liver-related procedures	57 (47.5)	54 (52.4)	0.503
Wedge resection	17 (14.2)	14 (13.6)	0.902
Portal lymph node dissection	25 (20.8)	38 (36.9)	0.008
En-bloc diaphragm resection	15 (12.5)	12 (11.7)	0.846
Median operation time (range), minutes	300 (135 – 665)	310 (75 – 714)	0.379
Median blood loss (range), ml	290 (0 – 4000)	250 (0 – 1800)	0.370
Pringle maneuver	107 (89.2)	90 (87.4)	0.678
Intraoperative transfusion	8 (6.7)	5 (4.9)	0.565
Intraoperative detection of air leak	10 (8.3)	64 (62.1)	<0.001

Data are expressed as absolute numbers (percentage) or medians (range).

Table 3

Comparison of postoperative outcomes in the Air Leak Test group vs. non-Air Leak Test group.

<i>Postoperative features</i>	Non-Air Leak Test group (n=120) n (%)	Air Leak Test group (n=103) n (%)	<i>p</i>
Overall morbidity	57 (47.5)	40 (38.8)	0.193
Major morbidity	21 (17.5)	14 (13.6)	0.424
<i>Liver related morbidity</i>			
Bile leak	13 (10.8)	2 (1.9)	0.008
Grade A	4 (3.3)	1 (1)	0.277
Grade B–C	9 (7.5)	1 (1)	0.022
Hepatic insufficiency	5 (4.2)	0	0.063
Perihepatic collection	6 (5)	1 (1)	0.127
Bleeding	1 (1)	0	0.353
Median LOS for all patients (range), days	7 (4 – 80)	7 (3 – 37)	0.721
Median LOS for patients with postoperative bile leak (range), days*	21 (8 – 83)	6 (5–7)	0.027
90-day mortality	2 (1.7)	1 (1)	1.000

Data are expressed as absolute numbers (percentage) or medians (range).

Abbreviations: LOS, length of (hospital) stay.

* This analysis included 15 patients with postoperative bile leak.

Table 4

Univariate analysis of risk factors of postoperative bile leak.

Variables	Any postoperative bile leak (n=15)		Postoperative Grade B–C bile leak (n=10)	
	n (%)	p	n (%)	p
Age	65 (n=51) < 65 (n=172)	3 (5.9) 12 (7)	1 (2) 9 (5.2)	0.461
Sex	Male (n=121) Female (n=102)	10 (8.3) 5 (4.9)	5 (4.1) 5 (4.9)	1.000
ASA score	2 (n=46) > 2 (n=177)	5 (10.9) 10 (5.6)	1 (2.1) 9 (5.1)	0.692
Previous PVE	Yes (n=81) No (n=142)	9 (11.1) 6 (4.2)	0.048 3 (2.1)	0.039
Indication	Hepatocarcinoma (n=30) Colorectal metastases (n=127) Biliary tumors (n=22) Other malignancies (n=20) Benign tumors (n=5) NET metastases (n=19)	2 (6.7) 8 (6.3) 3 (13.6) 1 (5) 1 (20) 0	0.469 5 (3.9) 2 (9.1) 1 (5) 0 0	0.754
Repeat hepatectomy	Yes (n=36) No (n=187)	3 (8.3) 12 (6.4)	3 (8.6) 6 (3.4)	0.169
Two-Stage hepatectomy	Yes (n=30) No (n=193)	3 (10) 12 (6.2)	3 (10.3) 10 (3.3)	0.108
Anatomic resection	Yes (n=160) No (n=63)	9 (5.6) 6 (9.5)	6 (3.8) 4 (6.3)	0.474
Extended hepatectomy	Yes (n=102) No (n=121)	10 (9.8) 5 (4.1)	0.092 2 (1.7)	0.046
Caudate resection	Yes (n=31) No (n=192)	5 (16.1) 10 (5.2)	0.041 6 (3.1)	0.035
Associated liver-related procedures	Yes (n=121) No (n=102)	5 (4.1) 10 (9.8)	0.111 6 (5.9)	0.518

Variables	Any postoperative bile leak (n=15)		Postoperative Grade B–C bile leak (n=10)			
	n (%)	p	n (%)	p		
Operation time	300 min	Yes (n=106) No (n=117)	8 (7.5) 7 (6)	0.641	5 (4.3) 5 (4.7)	1.000
IO Blood loss	250 ml	Yes (n=128) No (n=95)	11 (8.6) 4 (4.2)	0.196	7 (5.5) 3 (2.2)	0.523
Intraoperative transfusion		Yes (n=13) No (n=210)	2 (15.4) 13 (6.2)	0.214	1 (7.7) 9 (4.3)	0.459
Pringle maneuver		Yes (n=197) No (n=26)	14 (7.1) 1 (3.8)	1.000	9 (4.6) 1 (3.8)	1.000
Air Leak Test		Yes (n=103) No (n=120)	2 (1.9) 13 (10.8)	0.008	1 (1) 9 (7.5)	0.022
Intraoperative diagnosis of bile leak		Yes (n=74) No (n=149)	2 (2.7) 13 (8.7)	0.153	1 (1.4) 9 (6)	0.171
Non-tumor liver						
Portal Fibrosis		Yes (n=15) No (n=202)	2 (13.3) 13 (6.4)	0.278	1 (5.9) 9 (4.4)	0.555
Steatosis >30%		Yes (n=21) No (n=196)	0 15 (7.7)	0.372	0 10 (5)	0.606
Portal Inflammation		Yes (n=40) No (n=168)	2 (4.8) 13 (7.2)	0.741	2 (4.8) 8 (4.4)	1.000

Data are expressed as absolute numbers (percentage).

Abbreviations: ASA, American Society of Anesthesiologists; PVE, Portal Vein Embolization; IO, intraoperative.

Table 5

Multivariate analysis of risk factors and protective factors for postoperative bile leak.

Variables	Overall bile leaks		Grade B–C bile leaks	
	<i>p</i>	<i>OR (95% CI)</i>	<i>p</i>	<i>OR (95% CI)</i>
Previous PVE	NS	-	NS	-
Extended hepatectomy	0.021	3.806 (1.229 – 11.790)	0.029	6.203 (1.209 – 31.816)
Caudate resection	0.030	4.046 (1.142 – 14.334)	0.013	6.702 (1.490 – 30.146)
Non-Air Leak Test group	0.002	11.76 (2.40 – 58.82)	0.012	16.66 (1.83 – 142.85)

Abbreviations: OR, Odds Ratio; CI, confidence interval; PVE, portal vein embolization.