

# Bile Leakage and Liver Resection

## Where Is the Risk?

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**Hypothesis:** The knowledge of risk factors for bile leakage after liver resection could reduce its incidence.

**Design:** Retrospective study.

**Setting:** Tertiary care referral center.

**Patients:** The study included 610 patients who underwent liver resection from January 1, 1989, through January 31, 2003.

**Interventions:** Liver resections without biliary anastomoses.

**Main Outcomes Measures:** Bile leakage incidence and its correlation to preoperative and intraoperative patient characteristics.

**Results:** Postoperative bile leakage occurred in 22 (3.6%) of 610 patients. Univariate analysis showed that cirrhosis ( $P=.05$ ) or intraoperative use of fibrin glue ( $P=.01$ )

was associated with a lower incidence of bile leakage. Moreover, the following factors were significant predictors of bile leakage: peripheral cholangiocarcinoma ( $P<.001$ ), major hepatectomy ( $P=.03$ ), left hepatectomy extended to segment 1 ( $P<.001$ ), extension of transection out of the main portal scissure ( $P=.006$ ), and hepatectomy including segment 1 ( $P=.001$ ) or segment 4 ( $P=.003$ ). At multivariate analysis, use of fibrin glue was an independent protective factor (relative risk=0.38,  $P=.046$ ), whereas peripheral cholangiocarcinoma (relative risk=5.47,  $P=.02$ ) and resection of segment 4 (relative risk=3.10,  $P=.02$ ) were independent risk factors for bile leakage.

**Conclusions:** Hepatectomies including segment 4, especially if performed for peripheral cholangiocarcinoma, lead to a high risk for postoperative bile leakage. Intraoperative use of fibrin glue may reduce the risk of postoperative bile leakage.

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**A**S A RESULT OF IMPROVED surgical techniques and perioperative care, hepatic surgery has become safer in recent years, and the operative mortality rate has decreased.<sup>1-4</sup> Despite the decrease in overall postoperative complications, the incidence of bile leakage has not changed,

and the plane of liver transection have not yet been defined clearly. The aim of this study was to investigate the perioperative risk factors related to postoperative bile leakage, placing particular focus on anatomical and technical variables.

### See Invited Critique at end of article

ranging from 2.6% to 12% in recent large series.<sup>1,3,5</sup> Bile leakage is one of the most common complications after hepatic surgery, and it is associated with an increased rate of sepsis and liver failure, higher postoperative mortality, and longer in-hospital stay.<sup>5</sup> Risk factors for postoperative bile leakage<sup>5,6</sup> and the role of intraoperative tests to prevent it<sup>7,8</sup> are still debated. Relationships between the onset of bile leakage, the liver segments in-

involved in the resection, and the plane of liver transection have not yet been defined clearly. The aim of this study was to investigate the perioperative risk factors related to postoperative bile leakage, placing particular focus on anatomical and technical variables.

## METHODS

Prospectively collected clinical data on consecutive patients who underwent liver resection in our department from January 1, 1989, through January 31, 2003, were reviewed retrospectively. Patients with hepatectomies associated with extrahepatic bile duct resection and reconstruction and patients with intraoperative bile duct exploration were excluded.

## PROCEDURAL DETAILS

Preoperative diagnostic workup did not routinely include imaging of the biliary tree, which was performed only in the presence

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of cholestasis or biliary dilatation detected at ultrasonography or computed tomography. Intraoperative ultrasonography (SSD-1200 with 7.5-MHz intraoperative linear probe; Aloka Co, Ltd, Tokyo, Japan) was always performed as the first step to assess the site and extent of the disease, together with the relationship of the tumor with major intrahepatic vessels. During anatomical resection, extrahepatic inflow and outflow vascular control was routinely attained, when possible, with ligation and section of appropriate portal and arterial branches and hepatic veins. Continuous or intermittent pedicle clamping usually was performed during parenchymal transection; 207 liver resections were performed without pedicle clamping. The parenchymal transection was always performed by using a crushing clamp technique and absorbable clips (Absolok Extra; Ethicon Endo-Surgery, Inc, Cincinnati, Ohio) for any vessel or bile duct. Since 1999, we have used bipolar forceps with continuous irrigation before section of small vessels, and the number of absorbable clips has decreased. Segmental glissonian pedicles were always sutured during transection. During major liver resections, bile duct interruption usually was performed at the end of the parenchymal transection. Biliostasis was always checked by placing a white gauze on the transection surface. Intraoperative cholangiography or bile leakage tests, injecting isotonic solution through the cystic stump, and clamping the distal common bile duct were performed selectively at the end of parenchymal transection in patients suspected of having a bile duct lesion. When necessary, biliostasis was attained by suturing the identified bile leakage site with 5-0 or 6-0 absorbable monofilament (PDS II; Ethicon Inc, Somerville, NJ). When blood oozing from the raw cut surface persisted, hemostasis was achieved by applying fibrin glue (Tissocol/Tisseel; Baxter Healthcare, Deerfield, Ill). An abdominal drain usually was used. Most hepatectomies were performed by one of us (L.C.).

## DEFINITIONS

*Major hepatectomy* was defined as resection of 3 or more Couinaud segments. *Extended hepatectomy* was defined as resection of 5 or more Couinaud segments. *Bile leakage* was defined as the drainage of 50 mL or more of bile from the surgical drain, or from drainage of an abdominal collection, across 3 days or more. Nomenclature of segments and types of operations follow the Brisbane 2000 terminology.<sup>9</sup>

## STATISTICAL ANALYSIS

Continuous variables were reported as means and compared by using a *t* test. Categorical variables were compared by using the  $\chi^2$  or Fisher exact test, as appropriate. *P* < .05 was considered significant for all tests. The multivariate analysis was performed by including all the variables significant at univariate analysis into a stepwise regression model.

## RESULTS

### PATIENT CHARACTERISTICS

The analysis was performed in 610 patients without biliary anastomoses. Types of hepatectomy, classified according to Brisbane 2000 terminology,<sup>9</sup> are reported in **Table 1**. The indications for operation were as follows: 257 colorectal metastases, 214 hepatocellular carcinomas, 51 noncolorectal metastases, 47 benign diseases, 20

**Table 1. Types of Hepatectomy\***

Procedure	No.
Type of hepatectomy	
Anatomical resection	486
Nonanatomical resection	124
Major resection	254
Extended resection	59
Anatomical resections	
Right extended hepatectomy with/without segment 1	12/30
Left extended hepatectomy with/without segment 1	1/2
Right hepatectomy with/without segment 1	12/111
Left hepatectomy with/without segment 1	8/53
Left hepatectomy with segment 5	2
Left hepatectomy with segment 8 with/without segment 1	2/1
Central hepatectomy (segments 4, 5, and 8)	11
Bisegmentectomy	126
Segmentectomy	83
Other anatomical resections	32

\*Types of hepatectomy are classified according to the Brisbane 2000 terminology.<sup>9</sup> Associated minor resections are not included in the table.

gallbladder cancers, 15 peripheral cholangiocarcinomas, and 6 intrahepatic lithiases.

The mean age of patients was 61.7 years (range, 2-86 years), and 153 patients (25.1%) were 70 years or older; 369 patients (60.5%) were male, and 241 (39.5%) were female. Cirrhosis, confirmed by means of specimen examination, was present in 167 patients (27.4%).

### INCIDENCE OF BILE LEAKAGE AND COMPLICATIONS

Postoperative bile leakage occurred in 22 (3.6%) of 610 patients. The overall in-hospital mortality was 15 patients (2.5%). One patient (4.5%) with bile leakage died because of the onset of sepsis and liver failure; 14 patients (2.3%) without bile leakage died in the postoperative course (*P* = .52). The overall morbidity rate was 27.5% (168/610). Among patients with bile leakage, 4 had additional complications; the incidence of complications in the remaining patients was 24.8% (146 patients, *P* = .48). Mean in-hospital stay was significantly longer for patients with bile leakage (24.0 vs 11.4 days, *P* < .001). Conservative management was the initial bile leakage treatment in all patients. Bile leakage healed spontaneously in 15 patients (68.2%); the remaining 7 patients (31.8%) required additional treatments such as endoscopic sphincterotomy in 7, percutaneous drainage in 3, and reoperation in 2.

### BILE LEAKAGE SITE

The site of bile leakage was identified only in the 7 patients requiring additional treatment. The cut liver surface caused the bile leakage in 4 patients (limited resection of segment 8, right hepatectomy extended to segment 4a, right hepatectomy extended to segment 1, or central hepatectomy), and parahilar bile duct lesion caused the bile leakage in the other 3 patients (2 left hepatectomies and 1 left hepatectomy extended to segment 1).

**Table 2. Univariate Analysis: Preoperative and Intraoperative Factors**

Factor	No (%)		P Value
	Without Bile Leakage (n = 588)	With Bile Leakage (n = 22)	
<b>Patient characteristics</b>			
Mean age (range), y	61.65 (2-86)	63.18 (49-78)	.54
≥70, No. (%)	147 (25.0)	6 (27.3)	.82
≥75, No. (%)	55 (9.4)	3 (13.6)	.76
Sex, No. (%)			.56
Men	357 (60.7)	12 (54.5)	
Women	231 (39.3)	10 (45.5)	
Cirrhosis, No. (%)	165 (28.1)	2 (9.1)	.05
<b>Diagnosis, No. (%)</b>			
Benign diseases	46 (7.8)	1 (4.5)	.87
Hepatocellular carcinoma	210 (35.7)	4 (18.2)	.09
Peripheral cholangiocarcinoma	11 (1.9)	4 (18.2)	<.001
Gallbladder cancer	20 (3.4)	0	.78
Colorectal metastases	248 (42.2)	9 (40.9)	.91
Noncolorectal metastases	47 (8.0)	4 (18.2)	.19
<b>Intraoperative factors, No. (%)</b>			
Pedicle clamping	438 (74.5)	14 (63.6)	.25
Cholangiography	98 (16.7)	5 (22.7)	.46
Positive cholangiography	19 (3.2)	1 (4.5)	.73
Fibrin glue on cut surface	393 (66.8)	9 (40.9)	.01
Abdominal drain	482 (82.0)	21 (95.5)	.18

## UNIVARIATE ANALYSIS

### Preoperative Characteristics

Among patients' characteristics, only the presence of liver cirrhosis was associated with a significantly lower rate of bile leakage (2/167 [1.2%] vs 20/443 [4.5%],  $P=.05$ ). The incidence of bile leakage was significantly higher after resection for peripheral cholangiocarcinoma (4/15 [26.7%] vs other diagnoses 18/595 [3.0%],  $P<.001$ ) (**Table 2**).

### Intraoperative Factors

Use of the Pringle maneuver was not related to subsequent clinical bile leakage nor was positive extravasation at intraoperative cholangiography. Treatment of the raw cut surface with fibrin glue was the only statistically significant protective intraoperative factor for bile leakage (9/402 [2.2%] vs 13/208 [6.2%],  $P=.01$ ) (Table 2).

### Surgical Procedure

The incidence of postoperative bile leakage was similar after anatomical and nonanatomical resection. Bile leakage rate increased significantly after major hepatectomy: 14 (5.5%) of 254 vs 8 (2.2%) of 356 minor hepatectomies ( $P=.03$ ). Biliary complications were more frequent after left hepatectomy extended to segment 1 (3/10 [30.0%] vs 19/600 [3.2%],  $P<.001$ ), and the rate was significantly higher after any left hepatectomy with or without segment 1 (7/66 [10.6%]) than after right hepatectomy with or without segment 1 (2/123 [1.6%],  $P=.02$ ) (**Table 3**).

**Table 3. Univariate Analysis: Surgical Procedure**

Procedure	No (%)		P Value
	Without Bile Leakage (n = 588)	With Bile Leakage (n = 22)	
<b>Surgical procedure</b>			
Anatomical resection	468 (79.6)	18 (81.8)	.80
Nonanatomical resection	120 (20.4)	4 (18.2)	
Major resection	240 (40.8)	14 (63.6)	.03
Extended hepatectomy	54 (9.2)	5 (22.7)	.08
<b>Anatomical resections</b>			
Right extended hepatectomy	27 (4.6)	3 (13.6)	.15
Right extended hepatectomy with segment 1	11 (1.9)	1 (4.5)	.92
Left extended hepatectomy with or without segment 1	3 (0.5)	0	.22
Right hepatectomy	110 (18.7)	1 (4.5)	.16
Right hepatectomy with segment 1	11 (1.9)	1 (4.5)	.92
Left hepatectomy	52 (8.8)	4 (18.2)	.27
Left hepatectomy with segment 1	7 (1.2)	3 (13.6)	<.001
Central hepatectomy (segments 4, 5, and 8)	10 (1.7)	1 (4.5)	.87
Bisegmentectomy segments 2 and 3	64 (10.9)	1 (4.5)	.55
Segmentectomy	80 (13.6)	3 (13.6)	.76

## Transection Plane

For patients who underwent anatomical resections, we analyzed the relation between bile leakage and the transection planes involved during liver resection. Parenchymal transection through the intersegmental planes or the 3 portal scissures was not associated with an increased incidence of postoperative bile leakage. Nevertheless, the risk of bile leakage increased significantly when the transection plane was extended out of the main portal scissure during a major resection to attain a tumor-free surgical margin (3/15 [20.0%] vs 19/595 [3.2%],  $P=.006$ ); the bile leakage rate was higher when a right hepatectomy was extended to segment 4a or 4b (3/9 [33.3%] vs 19/601 [3.2%],  $P<.001$ ).

## Resected Segments

Hepatectomies including segments 1 and 4 were at high risk for postoperative bile leakage. Findings were as follows: segment 1 included was 11.5% (6/52) vs not included 2.9% (16/558,  $P=.001$ ); segment 4 included was 6.7% (14/208) vs 2.0% not included (8/402),  $P=.003$ ) (**Table 4**).

## MULTIVARIATE ANALYSIS

Multivariate analysis was performed; it included all factors significant at univariate analysis (liver cirrhosis, peripheral cholangiocarcinoma, treatment of the cut surface with fibrin glue, major hepatectomy, left hepatectomy extended to segment 1, resection including segments 1 and 4). Stepwise logistic regression analysis was used to identify resection of segment 4 and peripheral cholangio-

**Table 4. Univariate Analysis: Resected Segments**

Couinaud Segment	No. (%)		P Value
	Without Bile Leakage (n = 588)	With Bile Leakage (n = 22)	
1	46 (7.8)	6 (27.3)	.001
2	143 (24.3)	9 (40.9)	.08
3	160 (27.2)	10 (45.5)	.06
4	194 (33.0)	14 (63.6)	.003
5	285 (48.5)	9 (40.9)	.49
6	249 (42.3)	9 (40.9)	.89
7	236 (40.1)	9 (40.9)	.94
8	236 (40.1)	11 (50.0)	.36

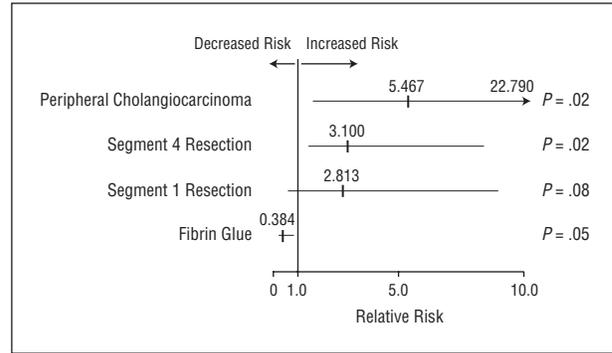
carcinoma as positive independent predictors for bile leakage and treatment of the cut surface with fibrin glue as an independent preventive factor, as shown in the **Figure**.

### COMMENT

Bile leakage incidence is not easily comparable in the reported series of hepatectomies because a worldwide accepted definition is lacking. In our series, the incidence is low, probably because of the care taken during the parenchymal section. Even if we encountered only 1 death related to bile leak in our series, bile leakage is still a serious complication because of increased length of hospital stay and septic complications.<sup>6</sup> Moreover, bile leakage is associated with an increase of as much as 40% in the postoperative mortality rate.<sup>10</sup> We hope that an improved understanding of associated risk factors can lead to further reductions.<sup>3</sup> Unfortunately, few articles on the risk factors for bile leakage after hepatectomy have been published, and few have focused on the technical and anatomical variables that may contribute to the risk of biliary complications.

Among preoperative factors, cirrhosis and peripheral cholangiocarcinoma are related significantly to the onset of bile leakage. Tanaka et al<sup>11</sup> also reported a lower incidence of bile leakage in patients with cirrhosis, but the difference was not statistically significant. In the present series, patients with cirrhosis presented an even lower rate of bile leakage during the postoperative course. Nevertheless, surgical procedures in patients with cirrhosis were less aggressive, with a lower rate of extended and major resections. Moreover, multivariate analysis results did not confirm liver cirrhosis as a protective factor for bile leakage. As previously reported,<sup>11</sup> our series also showed peripheral cholangiocarcinoma as an independent risk factor for bile leakage. In such cases, the tumor is often a large mass centrally located deep in the liver. Thus, tumor-free margins of resection usually can be achieved only with major or extended hepatectomies, with a transection plane that is often extended out of the portal scissures and with an extensive dissection of the hepatic duct close to the hilar confluence.<sup>12</sup>

The use of fibrin glue on the raw cut surface of the liver after resection had a protective effect on the incidence of bile leakage, in both the univariate and multi-



**Figure.** Multivariate analysis of risk factors and protective factors for postoperative bile leakage.

variate analyses. In 1996, Noun et al<sup>13</sup> reported the results of a French multicenter, randomized trial on the effectiveness of fibrin glue treatment after elective liver resections. Patients treated with fibrin glue had a mean bilirubin concentration in the drainage fluid that was significantly lower than that in the control group. Nevertheless, because of the small number of patients, the study could not demonstrate a lower incidence of bile leakage or abdominal collections after surgery. In the patients in our study, fibrin glue was applied on the raw cut surface to improve hemostasis during persistent blood oozing. Fibrin glue improved hemostasis and significantly reduced postoperative bile leakage rate. A larger, randomized trial is needed to confirm these interesting data.

The role of intraoperative bile leakage tests or cholangiography in predicting bile leakage is still debated. To our knowledge, only 1 randomized trial has been performed to investigate the value of a bile leakage test during hepatic resection.<sup>7</sup> Bile leakage was diagnosed and sutured during the operation in 41% of patients of the bile leakage test group; nevertheless, the incidence of bile leakage in the postoperative course was similar in the 2 groups (6% vs 4%). On the other hand, Yamashita et al<sup>13</sup> reported no bile leakages after 102 consecutive liver resections with an intraoperative test vs 31 leakages after 679 hepatectomies without intraoperative bile leakage test. The difference was statistically significant, but the study was not randomized and the 2 groups of patients were not operated on in the same period. In our study, intraoperative cholangiography or a bile leakage test was performed selectively only in patients suspected of having a bile duct lesion. In this group, the incidence of subsequent postsurgical bile leakage was similar to that in patients who did not undergo the procedure, suggesting that intraoperative tests could be useful in high-risk patients to reduce postoperative bile leakage. Nevertheless, biliary fistula cannot be completely identified and eliminated by the systematic use of intraoperative cholangiography or bile leakage test.

The relationship between type of hepatectomy and postoperative bile leakage has not yet been defined clearly. Authors of 2 previous articles<sup>5,6</sup> reported central hepatectomy (segments 4, 5, and 8); right anterior sectionectomy (segments 5 through 8); caudate lobectomy; and resections including segments 4, 5, and 8 as high-risk procedures for bile leakage. Nevertheless, the group of high-

risk hepatectomies is heterogeneous, and no single procedure was a significant risk factor. Lo et al<sup>10</sup> reported left-sided hepatectomy as an independent factor for the onset of postoperative bile leakage because of the risk of damaging a right posterior biliary duct draining into the left hepatic duct. In the present study, patients who underwent major hepatectomy had a higher incidence of postoperative bile leakage. Among all types of major liver resections, only left hepatectomy extended to segment 1 was a significantly high-risk procedure; when a classic left hepatectomy was performed, the risk for bile leakage did not increase.

The plane of parenchymal transection can be involved in the genesis of bile leakage. During anatomical resections, when the section of the parenchyma is performed through the intersegmental planes or the 3 portal scissures, the risk of bile leakage is low. Nevertheless, in our experience, the incidence of bile leakage increased significantly when the transection plane was extended out of the main portal scissure for oncological reasons, mainly if extended to segment 4a or 4b. Analysis of all surgical procedures showed that the risk for bile leakage could be increased when the resection was extended to segment 1 or 4. For this reason, we performed a further analysis, according to the segments included in the resections. The results of univariate and multivariate analyses confirmed that the resection of segment 4 was an independent risk factor for the development of postoperative bile leakage, whereas resection of segment 1 was borderline significant.

The bile duct confluence lies beneath segment 4, surrounded by a sheath representing the hilar plate. At the hilum, the bile duct and blood vessel branches penetrate the plate system in all segments, except for segment 4.<sup>14</sup> The segment 4 bile ducts usually join to form a single left medial segmental duct; the confluence patterns of the left intrahepatic bile ducts can vary. The segment 4 duct may enter the left hepatic duct close to the confluence or may join distally into the confluence of segment 2 and 3 ducts or into the segment 3 duct.<sup>15</sup> Hepatectomies that include segment 4 usually expose the major glissonian sheath and hepatic hilum on the cut surface, with a high risk of damaging the bile duct wall. All of the bile duct lesions at the hilum that were identified in our series came from left hepatectomies, regardless of whether they extended to segment 1, confirming the risk of bile leakage from the duct confluence during hepatectomies that include segment 4. When the scheduled resection includes segment 4, careful dissection of the glissonian sheath should always be performed by low-

ering the hilar plate, which can help to prevent bile duct lesions.

In conclusion, hepatectomies including segment 4, especially if performed for peripheral cholangiocarcinoma, place the patient at higher risk for postoperative bile leakage. Careful surgical technique is mandatory to avoid bile leakage. Lowering the hilar plate is helpful whenever segment 4 is resected. Treatment of the cut surface with fibrin glue reduces the risk of postoperative bile leakage. Use of these techniques is warranted to reduce bile leakage in hepatic resection.

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