

Posthepatectomy Bile Leakage: How to Manage

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Key Words

Bile leakage · Liver resection · Percutaneous transhepatic biliary drainage · Endoscopic stenting

Abstract

Background: Biliary leakage after liver resection continues to be reported. Management of bile leakage has changed in recent years, with nowadays non-surgical procedures as the preferred treatment. **Methods:** Biliary leakage and management were assessed in 381 patients who underwent liver resection between January 2005 and April 2011. **Results:** The overall rate of biliary leakage after liver resection was 5.0%, with a higher incidence in patients who had undergone concomitant hepaticojejunostomy (HJ; 13.6 vs. 3.2%). Hospital stay ($p = 0.047$), major resections ($p = 0.018$), operation time ($p = 0.011$), and relaparotomy ($p = 0.002$) were risk factors for postoperative bile leakage. Multivariate analysis identified relaparotomy as an independent factor (OR 4.216, $p = 0.034$). Bile leakage in patients without HJ ($n = 10$) was managed in 6 patients by percutaneous transhepatic biliary drainage (PTD), and in 3 patients by endoscopic drainage. One patient was treated surgically. All patients with an HJ and postoperative bile leakage ($n = 9$) underwent PTD. **Conclusion:** The incidence of posthepatectomy biliary leakage has decreased over time, while PTD and endoscopic stenting are effective treatment modalities. PTD is the treatment of choice in bile leakage after resection combined with HJ.

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Introduction

The numbers of hepatic resections are increasing. Although less overall postoperative complications are reported, biliary leakage after liver surgery continues to be documented with unchanged incidences, ranging from 3.6 [1] to 33% [2]. Biliary leakage may lead to intraperitoneal septic complications, liver failure and ultimately, death [3]. The incidence and management of bile leakage after partial liver resection in our Department from 1992 to 2004 has been reported by Erdogan et al. [4, 5]. However, the management of this complication has changed from relaparotomies to mainly non-surgical interventions in the last years, potentially leading to a decrease in procedure-related complications and better outcomes. Besides conservative treatment such as drainage and antibiotics, several management strategies are available, such as percutaneous and endoscopic drainage of bile leakage. The aims of this study were to evaluate the efficacy of management of bile leakage after liver resection, to examine the incidence and outcomes of bile leakage in patients with and without hepaticojejunostomy (HJ), and to assess the evolution of the treatment approach of postresectional biliary leakage in a recent period of time (2005–2011) as compared to the previous reported period 1992–2004.

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Methods

A retrospective analysis was performed of patients who received a liver resection in our Department between January 2005 and April 2011. This group was divided into patients who had undergone liver resection with or without concomitant bile duct resection and biliary-enteric reconstruction, usually an HJ. In all patients, demographics, preoperative data, operative variables, complications (including postoperative bile leakage and management), and revision surgery were evaluated retrospectively.

Definitions

Liver resections were classified as major, defined as resections of more than three Couinaud's segments, or minor, defined as resections of less than three liver segments, including wedge resections and metastectomies. Bile leakage was defined as continuous drainage of bile from the abdominal drain (>1 day after surgery), and/or leakage or a bile collection demonstrated on radiological imaging (ERC, US, CT), and/or detection of a bile collection drained percutaneously or during relaparotomy, as has been described previously [5]. Bile leakage originating from the cut surface of the remnant liver was reported as peripheral bile leakage, and leakage from the extrahepatic bile ducts as central bile leakage.

No commonly used definition of posthepatectomy bile leakage has been established, resulting in a wide range of reported bile leakage rates. However, Koch et al. [6] recently published a grading system of bile leakage after hepatobiliary and pancreatic surgery. In-hospital mortality was defined as death within 30 days from operation or thereafter if the patient was still hospitalized.

Management of Postoperative Bile Leakage

Conservative management (prolonged drainage and antibiotic treatment in case of persistent fever) constituted initial treatment of postoperative bile leakage. Additionally, percutaneous drainage, usually with antimicrobial therapy, was undertaken if an intra-abdominal bile collection sustained, as identified by abdominal ultrasonography and/or CT scan. In case of persistence of biliary leakage, ERC with sphincterotomy and stent placement in the CBD was undertaken. If non-surgical treatment proved not to be effective, the clinical situation of the patient worsened, or biliary peritonitis developed, a relaparotomy with drainage of the bilioma/bile leak was considered.

Statistical Analysis

Values are expressed as means \pm SD, unless otherwise stated. The differences among the groups were compared using the two-tailed unpaired Student *t* test for continuous parametric data. The Mann-Whitney *U* test was used for continuous nonparametric data. Categorical data were compared using the Fisher exact test or χ^2 test, as appropriate. Firstly, univariate analysis was performed to examine variables significantly correlated with postoperative bile leakage. Significant factors on univariate analysis were then analyzed by stepwise logistic regression to identify independent predictors of bile leakage. The results were considered to be of statistical significance when $p < 0.05$. The data were analyzed by statistical software (SPSS 18.0.0; SPSS, Chicago, Ill., USA) and GraphPad Prism (Graph-Pad Software, San Diego, Calif., USA).

Results

In the most recent period from 2005 to 2011, 381 hepatectomies were performed, compared to 286 liver resections in the previous period between 1992 and 2004. Colorectal metastases were seen most frequently, in 132 of all patients (34.6%) in the first group (2005–2011) and 51.7% (121/234) in the second (1992–2004; $p < 0.001$). A higher rate (30.2%, 115/381 vs. 26.5%, 62/234) of benign lesions was seen in the patients operated between 2005 and 2011 ($p < 0.001$).

Overall, the complication rate of biliary leakage after liver resection in the more recent years (2005–2011) was 5.0% (19/381 patients) compared to 10.8% (31/286 patients) in the previous period (1992–2004) [5]. In the more recent period, the incidence of bile leakage was much higher in patients who underwent concomitant HJ as compared to those without HJ, i.e. 13.6% ($n = 66$) and 3.2% ($n = 315$), respectively.

In the more recent group, all patients with postoperative bile leakage had significantly longer hospital stay (median 15.0, IQR 11.0–20.0 days vs. 9.0, IQR 7.0–12.3 days; $p < 0.001$), had undergone more major resections (74%, 14/19 vs. 44%, 151/340; $p = 0.013$), had significantly longer operation time (median 378, IQR 228–439 min vs. 227, IQR 155–349 min; $p = 0.003$), and more often underwent a relaparotomy (21%, 4/19 vs. 3.9%, 14/262; $p = 0.009$), compared to patients without biliary leak. No significant differences were found for age, gender, comorbidity, compromised liver, preoperative portal vein embolization, unresectability, readmission time, or in-hospital mortality. However, taking into account only the patients without HJ, significant differences were found for age ($p = 0.012$), and relaparotomy ($p < 0.001$). No other significant differences were seen. These patient characteristics are shown in table 1.

In the more recent group, hospital stay (OR 1.031, $p = 0.047$), major resections (OR 3.505, $p = 0.018$), operation time (OR 1.003, $p = 0.011$), and relaparotomy (OR 6.629, $p = 0.002$) were overall risk factors associated with postoperative bile leakage, as determined by univariate analysis. Multivariate analysis identified only relaparotomy as independent factor that was significantly correlated with the occurrence of bile leakage (OR 4.216, $p = 0.034$, 95% CI 1.11–15.97). In patients without HJ, in univariate analysis, relaparotomy (OR 25.714, $p < 0.001$) and age (OR 0.950, $p = 0.016$) were significant factors for biliary leak, with relaparotomy again as only independent factor (OR 19.599, $p = 0.001$; 95% CI 3.48–110.38). The distribution of bile leakage according to type of hepatic re-

Table 1. Patient characteristics pre- and postoperatively (without HJ; 2005–2011)

Variable	No bile leakage	Bile leakage	p value
Total	305/315 (96.8)	10/315 (3.2)	
Age, years	55.1 ± 14.6	43.0 ± 22.1	<0.001*
Males	121/305 (39.7)	3/10 (30)	0.745
Comorbidity	290/305 (95.1)	10/10 (100)	1.000
Compromised liver	180/305 (59.0)	8/10 (80.0)	0.326
Cirrhosis	12	0	
Steatosis	106	5	
Fibrosis	95	3	
Cholestasis	23	2	
Hospital stay, days	9.0 ± 9.1	12.0 ± 10.3	0.100
Portal vein embolization	20/305 (6.6)	2/10 (20.0)	0.149
Major resection	103/284 (36.3)	5/10 (50)	0.506
Unresectable	21/305 (6.9)	0/10 (0)	1.000
Operation time, min	213 ± 110	248 ± 100	0.146
Relaparotomy	5/305 (1.6)	3/10 (30.0)	0.001*
Readmission time, days	9 (4–42)	9 (5–12)	1.000
Intrahospital mortality	12/305 (3.9)	0/10 (0)	1.000

Asterisk indicates statistically significant difference. Figures in parentheses indicate percentages or IQR. Values for age are expressed as mean ± SD, and for hospital stay, operation time and readmission time as mean + SD.

section is depicted in table 2. Most bile leakages were seen in patients who had undergone right hemihepatectomy.

Between 2005 and 2011, bile leakages (n = 10) in patients without HJ were non-surgically managed in 9 patients (90%) and surgically in one patient (10%). The latter was a 4-year-old child with a traumatic liver laceration and leakage of the extrahepatic bile duct, which was sutured. However, bile leakage persisted; therefore, a left hemihepatectomy was ultimately performed (hospital stay 30 days). Six patients were managed by percutaneous biliary drainage (PTD) with a mean hospital stay of 9.8 ± 1.4 days and 3 patients by endoscopic drainage (fig. 1) with a mean hospital stay of 12.0 ± 3.0 days. An HJ had to be performed in one patient after a right hemihepatectomy with postoperative bile leakage due to transection of an aberrant isolated left segmental bile duct arising from the right ductal system, which could obviously not be treated by endoscopic retrograde cholangiopancreatography (ERCP) and placement of an endoprosthesis. Another patient developed persistent bile leakage after extirpation of an intrahepatic choledochal cyst. During

Table 2. Type of liver resection in patients with bile leakage (2005–2011)

Surgery	Without HJ (n = 10)	With HJ (n = 9)
Major		
Right hemihepatectomy	4 (40%)	5 (56%)
Right extended hemihepatectomy	0	0
Left hemihepatectomy	0	2 (22%)
Left extended hemihepatectomy	0	0
Minor		
1–2 segments	3 (30%)	1 (11%)
Wedge resection	0	0
Other	3 (30%)	1 (11%)

Table 3. Treatment of bile leakage over time in patients without and with HJ (2005–2011)

Treatment bile leakage	Without HJ (n = 10)	With HJ (n = 9)
Percutaneous radiological drainage	6 (60%)	9 (100%)
Endoscopic drainage	3 (30%)	0
Conservative treatment	0	0
Sutured	1 (10%)	0

ERCP, there was no connection between the central bile duct and the bile ducts of the right liver. Therefore, a right hemihepatectomy was performed, again complicated by bile leakage from the proximal end of the left main duct. Stent placement during ERCP was required twice (after 11 and 21 days) in this patient. Finally, the stent was removed after 83 days. None of the patients was managed medically. All of the patients with an HJ and postoperative bile leakage (n = 9) underwent PTD. All treatment strategies are summarized in table 3.

Of the previous series (1992–2004), including only patients who had liver resection without HJ, all patients (n = 16) with postoperative bile leakage were managed non-surgically. In 13 patients (81.3%), an intervention was carried out; 4 (25%) patients were treated by percutaneous radiological drainage with a mean duration of 13 days, and 9 (56.3%) patients were managed by endoscopic drainage with a stent (mean 11 days). The remaining 3 patients (18.8%) were managed conservatively, and bile leakage resolved after a maximum time of 18 days.

No in-hospital mortality was seen in patients with bile leakage after liver resection with or without HJ. An over-

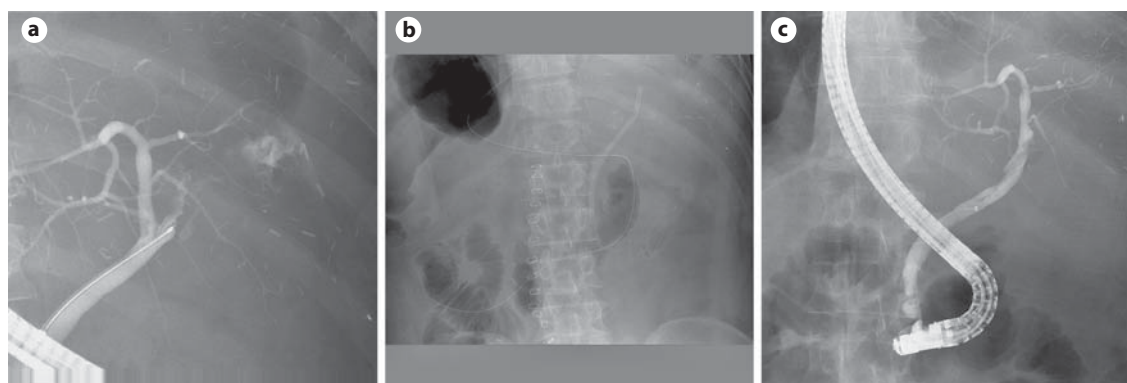


Fig. 1. **a** Endoscopic retrograde cholangiopancreatography showing biliary leakage of the stump of the right hepatic duct after right hemihepatectomy. **b** ERCP with stent placement. **c** Six weeks later, bile leakage subsided.

Table 4. Complications and relaparotomies after initial treatment, listed according to diagnosis (2005–2011)

Diagnosis	Initial treatment	Complication	Relaparotomy
Colorectal metastases	Percutaneous drainage	Subphrenic abscess	Drainage
Focal nodular hyperplasia	ERCP	Persistent bile leakage	HJ
Choledochal cyst	ERCP	Persistent bile leakage	Right hemihepatectomy
Traumatic laceration	Suture	Persistent bile leakage	Left hemihepatectomy

view of the relaparotomies is shown in table 4. In the recent period 2005–2011, of the patients without HJ who did not have postoperative bile leakage (table 1), 5 (1.6%) underwent a relaparotomy, and 12 (3.8%) died in the hospital, compared to 3.2 and 2.8%, respectively, in the preceding period 1992–2004.

According to the abovementioned system proposed by Koch et al. [6], in our study 16 patients (7 patients without HJ, and 9 patients with HJ) belonged to grade B and 3 patients (without HJ) to grade C. No grade A bile leakages were observed (table 5). This grading system is, therefore, useful in selecting patients with postoperative bile leakage who are candidates for radiological intervention (grade B) or laparotomy (grade C).

Although no patients were managed conservatively between 2005 and 2011, in 18.8% of patients treated in the previous period (1992 and 2004) the bile leakages resolved spontaneously, thus leaving the grade A patients for conservative treatment. The definition of Koch et al. [6] is not only based on the need for radiological intervention or relaparotomy; a three times higher concentration of bilirubin in the drain or intra-abdominal fluid compared to the serum bilirubin concentration on the same

day is used. In our series (2005–2011), bilirubin concentration in the drain fluid was measured in only 6 patients, 2 of whom showed a three times greater value in the abdominal drain fluid. In our opinion, assessment of bilirubin concentration in the drain fluid has no additional value in this grading system. Regarding the internationally validated classification system introduced in 2004 by Dindo et al. [7], 16 patients (7 patients without HJ and 9 patients with HJ) in our analysis were classified as grade IIIA, and 3 patients as grade IIIB, which is similar to the group of Koch et al. [6]. In all, these classification systems are effective and may facilitate the evaluation of therapeutic strategies for biliary complications. Nevertheless, it is important to note that patients with minor bile leakage may not have been included because of spontaneous resolution of the bile leak.

Discussion

The incidence of posthepatectomy biliary leakage has decreased in recent years from 10.8 to 5.0%. Patients in whom liver resections were performed with concomitant

Table 5. Proposal of the International Study Group of Liver Surgery for grading bile leakage after hepatobiliary surgery

Grade	Description	AMC
A	Bile leakage requiring no or little change in patient's clinical management	0
B	Bile leakage requiring a change in patient's clinical management (e.g. additional diagnostic or interventional procedures) but manageable without relaparotomy, or a grade A bile leakage lasting for >1 week	16
C	Bile leakage requiring relaparotomy	3

AMC = Academic Medical Center.

HJ showed a higher rate of postoperative bile leakage in our series (2005–2011: 13.6 vs. 3.2% and 1992–2004: 28.9 vs. 6.8%). Obviously, these patients had a higher risk of biliary leakage because of the additional bilioenteric anastomosis. In patients with only liver resection, bile leakage from the transected liver surface or from intraoperative ductal injury of the central bile ducts was the cause of postoperative bile leakage. Bile leakage after hepatectomy is still one of the most frequently reported complications after liver resection, with incidences reported in the literature of 3.6% in patients without biliary anastomoses to 33% in patients with cholangiocellular carcinoma also without biliary reconstruction. In this study, the incidence of bile leakage in patients without HJ is in the lower limits of previously reported results.

To our knowledge, only few studies published the results of bile leakage after liver resection with concomitant biliary reconstruction [8, 9]. A recent report showed the results of patients who underwent liver resection with biliary reconstruction compared to patients without biliary anastomosis [8]. Bile leakage was seen in 21.0 and 4.6%, respectively; an almost similar finding as in our study.

Many authors reported that conservative management is the preferred treatment in patients with postoperative bile leakage after liver resection without HJ, citing high success rates (up to 76.2%) [8]. Others also have suggested conservative management in patients with bile leakage after liver resection with HJ [9, 10]. In our series, no patients in the period 2005–2011 were managed without intervention (PTD/ERCP). However, there is a possible bias because bile leakages may have resolved spontaneously without having been noted during admission. Non-surgical treatment is becoming the preferred ap-

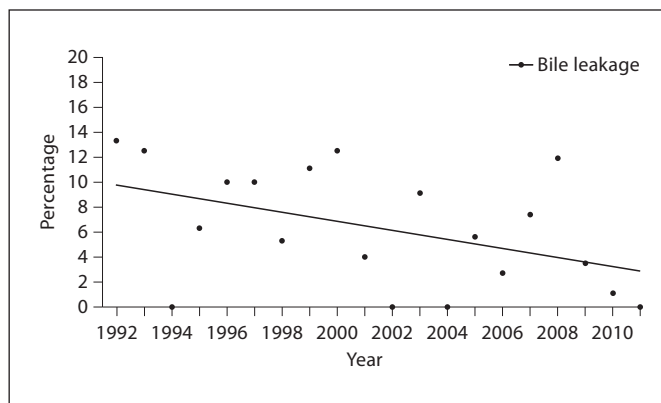


Fig. 2. The incidence of bile leakage decreases over time.

proach in the management of postoperative bile leakage [11]. This is confirmed by the results of this study, in which all patients with bile leakage were successfully treated by percutaneous or endoscopic drainage between 2005 and 2011.

The risk factors for bile leakage have been already extensively described in several studies [1, 5, 11–16]. Reported independent factors that were correlated with the occurrence of bile leakage were: (1) exposure of Glisson's sheath on the cut surface (caudate lobectomy, central bisectonectomy, and right anterior sectionectomy); (2) resection of segment 4; (3) a cut surface area $\geq 57.5 \text{ cm}^2$; (4) repeated hepatectomy; (5) intraoperative blood loss $\geq 775 \text{ ml}$; (6) intraoperative bile leakage; (7) prolonged operative time $\geq 300 \text{ min}$; (8) peripheral cholangiocarcinoma, and (9) preoperative chemoembolization. Bile leakage was also associated with male gender, advanced age, tumor size, major hepatectomy, right-sided hepatectomy, left hepatectomy extended to segment 1, surgical irradicality, duration of vascular occlusion, and red cell transfusion [1, 5, 11–16]. In our study, relaparotomy was the only independent significant risk factor associated with bile leakage, a similar finding as found in the studies of Hayashi et al. [12] and Yoshioka et al. [16]. However, our multivariate analysis is based on small sample sizes (patients with bile leakage), resulting in possible bias.

Fibrin sealants have become widely used as topical hemostatic agents in liver surgery. However, the additional value to reduce biliary leakage is still controversial. A prospective, randomized controlled study showed that there was no difference in postoperative outcomes between patients who underwent liver resection with and without application of fibrin sealant [17]. There is no evi-

dence at the moment for routine use of fibrin sealant, which is supported by the abovementioned study. However, usually, the use of a fibrin sealant is determined by the surgeon's preference.

In conclusion, the incidence of posthepatectomy biliary leakage has been decreasing over time (fig. 2); however, it is still a common complication after liver resection. PTD and/or endoscopic stenting are effective in the treatment of most cases of biliary leakage in patients without HJ. Percutaneous abdominal drainage for bile collections is increasingly being performed. Treatment of the leak via PTD is also being increasingly adminis-

tered, whereas the number of cases of endoscopic drainage is decreasing. Surgical treatment is required when conservative treatment or radiological management fails. The incidence of relaparotomies has not changed; however, mortality seems to have declined over time. No mortality has been reported in patients with biliary leakage in the last period (2005–2011). Prompt percutaneous, transhepatic biliary drainage is the treatment of choice for bile leakage after HJ in combination with liver resection, and can be performed safely without the risk of mortality or the need for additional relaparotomies.

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