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Risk Factors and Management of Bile Leakage after Hepatic Resection

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Abstract. The aim of this study was to identify the perioperative risk factors for postoperative bile leakage after hepatic resection and to propose a treatment strategy for such leakage when it does occur. Between 1992 and 2000 a total of 313 hepatic resections without choledocojejunal anastomosis were performed at our institute. Risk factors related to bile leakage were identified with univariate analysis, and strategies were evaluated in relation to the findings of postoperative fistulography. Postoperative bile leakage developed in 17 patients (5.4%). Univariate analysis identified high risk factors as advanced age, a wide surface area of the incision (bile leakage group versus no bile leakage group: 102.1 vs. 66.4 cm^2, $p < 0.05$), and exposure of Glisson's sheath at the cut surface (e.g., central bisegmentectomy, S4, S8 subsegmentectomy). Groupings of patients by their postoperative fistulography results showed that patients with involvement of the proximal bile duct were slower to heal than those with no demonstrable bile duct involvement. The one patient whose fistulogram demonstrated peripheral bile duct involvement had uncontrollable leakage and required reoperation. Hepatectomies with a wide surface area and those that expose the major Glisson's sheath present serious risk factors for bile leakage. When the fistulogram shows proximal bile duct involvement, endoscopic nasobiliary tube drainage is necessary; when the fistulogram shows peripheral bile duct involvement, reoperation is needed.

Postoperative morbidity associated with liver surgery has decreased because of recent advances in the understanding of hepatic anatomy and physiology, together with improvements in perioperative management. Despite a significant decrease in overall operative morbidity, however, the rate of biliary complications has not changed, with an incidence of 4.8% to 8.1% reported in recently reported large series [1–6]. Bile leakage predisposes the patient to the development of sepsis, a well known cause of liver failure and death [7, 8]. The goal of our retrospective study was to identify the perioperative risk factors for postoperative bile leakage after hepatic resection and to propose a treatment strategy for such leakage.

Patients and Methods

We reviewed the medical records of the 313 patients who underwent hepatic resections without choledocojejunal anastomosis in the Second Department of Surgery at Yokohama City University Hospital between 1992 and 2000. There were 211 male and 102 female patients with a mean age of 62.9 years (range 23–84 years). The indications for hepatic resection and the rate of postoperative bile leakage are shown in Table 1. The one hepatic resection that included extrahepatic bile resection and reconstruction was excluded from this study.

Surgical Techniques

Thorough intraoperative ultrasonography was performed to determine the extent of disease and the line of parenchymal transection. Preoperative cholangiography usually was not performed. Intermittent Pringle's maneuvers or hemivascular occlusions were applied during almost all hepatic resections. From 1992 to 1998, only the SONOP SUS201D dissector (Aloka, Tokyo, Japan) was used to transect the liver parenchyma; since 1999 the CUSA system (Valley Lab, Boulder, CO, USA) and bipolar irrigation electrocautery (Codman & Shurtleff, Randolph, UA, USA) have been used.

Intraoperative cholangiography and bile leakage tests were routinely performed in all primary cases. The leakage test was performed by injecting approximately 5 to 10 ml of indigo carmine solution by means of an intraoperative cholangiography (IOC) balloon catheter 6 French in diameter (Fuji Systems, Tokyo, Japan). With this procedure we could recognize small bile leakage sites on the cut liver surface and could repair these sites, mainly by Z-suturing using 5-0 or 6-0 Prolene (Johnson & Johnson k.k. Tokyo, Japan). Fibrin glue was applied to the raw surface of the liver to promote hemostasis and to prevent occult bile leakage. Drains were removed when the drainage was serous and not bile-stained, usually around the fifth postoperative day.

Definitions

Diagnoses of biliary complications were based on postoperative findings of one or more of the following: (1) drainage of bile from the abdominal wound and drain, with the level of total bililubin in the discharge fluid more than 5 mg/ml or three times the serum level; (2) intraabdominal collection of bile confirmed by percutaneous drainage; (3) cholangiographic evidence of bile leakage.

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Table 1. Indications for hepatic resections and incidence of bile leakage.

Diagnosis	No.	Bile leakage
Hepatocellular carcinoma	126	9 (7.1%)
Metastatic liver tumor	187	8 (4.3%)
Total	313	17 (5.4%)

Risk Factors

To identify the perioperative risk factors for postoperative bile leakage after hepatic resection, 313 patients with and without bile leakage were compared with respect to patient and surgical variables. There were 14 patient variables: sex; age; hepatitis B antigen; hepatitis C antibody; hemoglobin level; white blood cell count; prothrombin test; serum levels of total bilirubin, asparaginic acid aminotransferase, and alanine aminotransferase, nutritional index (NSRI), where NSRI = albumin × 10+ lymphocytes × 0.005; hepaplastin test; liver cirrhosis; indocyanine green retention rate at 15 minutes; Child grade. There were also 6 surgical variables: operating time; amount of blood loss; total ischemic time; weight of the specimen; area of cut surface; and operative procedure.

Measuring the Area of the Cut Surface

The cut surface of the obtained specimen was traced on paper, and the traced area was scanned with the laser scanner. The corresponding area was calculated by computer.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation and compared using Student's *t*-test. Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate. All statistical analyses were performed using Stadt View 5.0 (Abacus, Berkeley, CA, USA), and $p < 0.05$ was considered statistically significant.

Patients with postoperative bile leakage were classified into four groups according to the postoperative fistulogram and biliary scintigram so we could analyze their clinical course and evaluate their management. The groups were as follows: type A, minor leakage, with only a small amount of bile leakage or an amount that decreased daily: type B, major leakage due to insufficient closure of the bile duct stump: type C, major leakage due to injury of the bile duct; type D, division of the bile duct. Figure 1 shows examples of each type.

Results

Incidence

Postoperative bile leakage developed in 17 (5.4%) of the 313 patients with hepatic resection. None of these 17 patients died in the hospital.

The relations between the types of hepatectomy and bile leakage are shown in Table 2. With hepatectomies in which the cut surface exposed the major Glisson's sheath and included the hepatic hilum, i.e., anterior and central segmentectomy, the S4, S5, and S8 subsegmentectomies were found to have the highest incidence of bile leakage. The major Glisson's sheath is exposed on the cut surface,

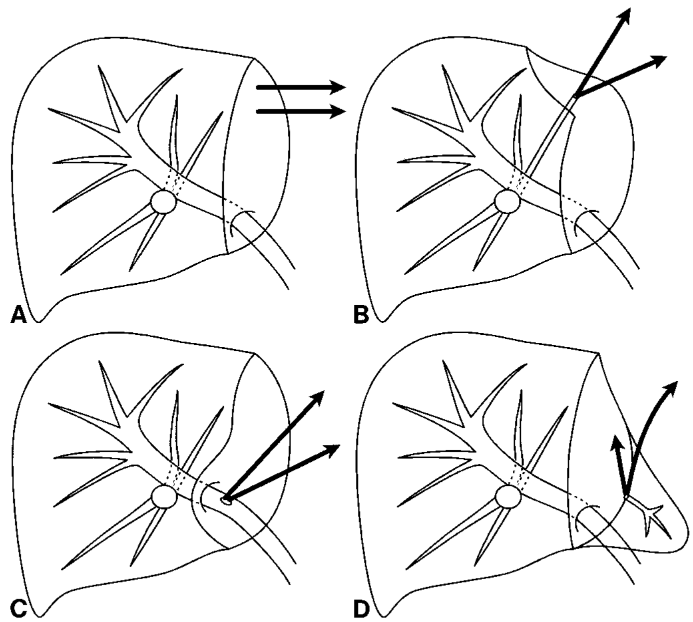

Fig. 1. Patients with postoperative bile leakage were classified into the following four groups: type A, minor leakage, with only a small amount of bile leakage; type B, major leakage due to insufficient closure of the bile duct stump; type C, major leakage due to injury of the bile duct; type D, major leakage due to division of the bile duct.

Table 2. Operative procedure correlated with bile leakage.

Operative procedure	Bile leakage (+), $n = 17$	Bile leakage (−), $n = 296$
Partial resection	2 (12%)	101 (34.1%)
Subsegmentectomy	6 (35%)	43 (14.5%)
Lateral segmentectomy	0	27 (9.1%)
Segmentectomy	5 (29%)	34 (11.5%)
Lobectomy	3 (18%)	65 (22.0%)
Extended lobectomy	1 (6%)	26 (8.8%)

and there are many opportunities for damaging it with the ultrasonic surgical aspirator. Therefore we designated these procedures "high risk." The relations between the types of hepatectomy and the mean area of the cut surface are shown in Table 3. Among of these hepatectomies, the cut surface areas seen with subsegmentectomy and segmentectomy were larger than that seen with partial resection hepatectomy (97.6 ± 40.7 and 87.0 ± 33.7 cm vs. 57.1 ± 32.8 cm; $p < 0.001$).

Risk Factors

Univariate analysis indicated that advanced age, large incisional surface areas, and high risk operations as described above were associated with the development of bile leakage (Table 4).

Management and Outcome

The clinical course and characteristics of bile leakage according to the patients' fistulograms and biliary scintigrams are shown in Table 5. Postoperative fistulograms were obtained from 11 patients. In five patients the fistulograms showed no demonstrable

Table 3. Operative procedure correlated with the cut surface area.

Operative procedure	Cut surface area (cm^2)
Partial resection	57.1 ± 32.8
Subsegmentectomy	97.6 ± 40.7
Lateral segmentectomy	25.3 ± 9.9
Segmentectomy	87.0 ± 33.7
Lobectomy	71.4 ± 36.5
Extended lobectomy	74.6 ± 39.3

Table 4. Factors associated with development of biliary leakage using univariate analysis.

Variable	Bile leakage (+), $n = 17$	Bile leakage (−), $n = 296$	p
Age (years)	70.1	61.7	< 0.01
Cut surface area (cm^2)	102.1	71.5	< 0.05
High risk operation (%)	47	17	< 0.01

Table 5. Fistulographic findings and outcome.

Presence of bile duct	No. ($n = 11$)	Duration of treatment after hepatectomy (days)
Negative	5	37.8
Positive	6	91.3
Proximal bile duct	5	102.6
Bile drainage (+)	2	30.0
Bile drainage (-)	3	179.2
Distal bile duct (+)	1	80.0 (Operation)

involvement of the bile duct. In these patients leakage was controllable by drainage with irrigation, and they healed, on average, within 37.8 days (range 7–64 days). The worst of these cases was further complicated by postoperative ascites, delaying the cessation of leakage up to 64 days. In the other six patients the fistulograms showed demonstrable involvement of the proximal bile duct. In these patients the bile leakage ceased, on average, within 102.6 days (range 29–264 days), the healing time of patients with intraoperative T-tube drainage being markedly shorter than that of those without it (30 vs. 179 days). The worst of these cases was complicated by stasis of the bile duct, causing bile leakage to persist until day 264. Another patient had demonstrable involvement of a peripheral bile duct. He underwent left lobectomy and then after 80 days left caudate lobectomy because the leakage was ultimately intractable.

Discussion

Bile leakage is, of course, the primary complication after liver surgery; not only can it debase the quality of the postoperative course, it can lead to hospital death. Our data demonstrated a 5.4% incidence of bile leakage, which was within the incidence range of 4.8% to 8.1% recently reported for large series [1–6].

Several studies have evaluated the risk factors for bile leakage after hepatic resection, with conflicting results. Lo et al. [6] reported that risk factors for bile leakage were advanced age, high preoperative white blood cell count, left side hepatectomy, and prolonged operating time. Yamashita et al. [9] concluded that operative procedures exposing the major Glisson's sheath and including the hepatic hilum constituted an independent risk factor. Using univariate analysis, our data showed that advanced age, a large incisional surface area, and high risk operations were risk factors for the development of bile leakage. Some reports have found age to be a risk factor for morbidity after hepatic resection [6, 10], whereas others have found no significant association. Lo et al. [6] found that intraabdominal infection after hepatic resection was more common in the elderly and that infection may precipitate biliary leakage by inducing tissue necrosis. The exact cause of the higher incidence of bile leakage in older patients was not apparent in our study. With regard to operative procedures, we believe that those during which there are many opportunities for damaging Glisson's sheath with the ultrasonic surgical aspirator pose a "high risk" to the patient; in such cases, the forceps fracture method should be used carefully when transecting the hepatic parenchyma, especially around Glisson's sheath.

Based on postoperative fistulograms and scintigrams, bile leakage can be classified into four groups: For the minor leakage group (type A) radiology shows no bile duct involvement. For the major leakage groups (types B and C), radiologically there is evidence of proximal bile duct involvement, as shown by leakage from the main biliary duct (the stump in type B and the side in type C). Type D comprises those whose fistulograms show peripheral bile ducts, in which case bile leakage continues from a small segregated segment of the liver because it lacks communication with the main biliary tree. The results of our data analysis showed that patients whose fistulograms showed proximal bile ducts (types B and C) took longer to heal than those without bile duct involvement (type A) (102.6 vs. 37.8 days). The single patient with a demonstrable peripheral bile duct (type D) suffered from uncontrollable leakage and required reoperation. These data demonstrate that fistulograms are helpful for determining the type of biliary leakage and the degree to which leakage can be controlled by drainage.

Some studies [11–15] have reported that endoscopic treatment [endoscopic papillotomy, endoscopic nasobiliary tube drainage (ENBD), and biliary stent] has been successful. Our data showed that the patients who underwent biliary drainage had markedly shorter healing times than those who did not (30 vs. 179 days), supporting the conclusion that biliary drainage is useful in such cases. Nasobiliary tubes seem to have special advantages, such as early fluoroscopic detection of the status of leakage, easy removal without repeated endoscopy, and preservation of papillary function. Patients may find prolonged treatment with nasobiliary tubes uncomfortable, so the use of these tubes should be limited to those with demonstrable proximal bile duct involvement who have biliary stasis. In addition, a recent study [9] reported that fibrin glue or ethanol injection to the fistula is particularly useful in cases in which surgical management has been difficult or has failed.

Based on these findings, we devised a treatment strategy for postoperative bile leakage after hepatic resection (Fig. 2). For type A patients, minor leakage is controllable by drainage and irrigation alone. Types B and C present complicated major bile leakage, and the problems in almost all of these patients are intractable, especially when accompanied by biliary stasis. When biliary stasis is seen on scintigraphy, these patients require ENBD. For the type D patient, ethanol or fibrin glue injection into the damaged bile duct of the segregated segment together with reoperation (damaged bile duct resection with reconstruction and hepatic resection of the segregated segment) is ideal; however, reoperation is likely to be difficult owing to the presence of dense adhesions.

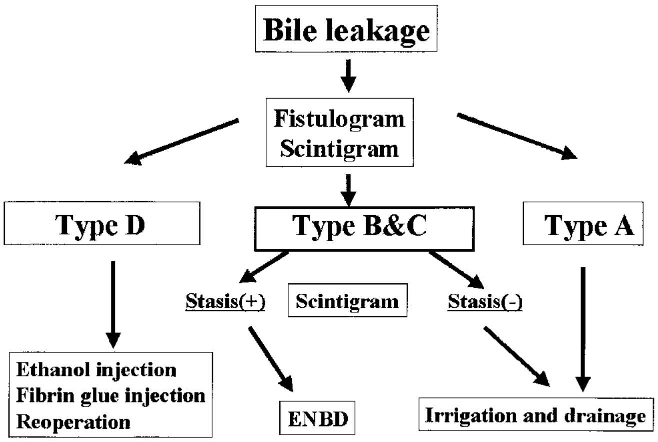

Fig. 2. Type A was controllable by drainage and irrigation alone. Types B and C had complications with major bile leakage. Almost all of these problems tended to be intractable, especially when biliary stasis was present. Endoscopic nasobiliary tube drainage (ENBD) was necessary for biliary drainage when biliary stasis is revealed on biliary scintigraphy. For type D patients ethanol or fibrin glue injection into the damaged bile duct of the segregated segment and reoperation are ideal.

Conclusions

Hepatectomies with a wide surface area and those that expose the major Glisson's sheath place the patient at serious risk for bile leakage. Therefore the forceps fracture method should be used carefully when transecting the hepatic parenchyma, especially around Glisson's sheath.

When biliary leakage occurs, most patients can be treated conservatively or with ENBD. However, those with peripheral bile duct involvement revealed by fistulography have a grave prognosis, and surgical treatment should be considered.

Résumé. Le but de cette étude a été d'identifier les facteurs de risque périopératoire de fuite biliaire après résection hépatique et de proposer une stratégie thérapeutique. Entre 1992 et 2000, 313 résections hépatiques sans anastomose cholédochojéjunale ont été réalisées dans notre établissement. Les facteurs de risque en rapport avec une fuite bilieuse ont été identifiés par analyse univariée, et les stratégies ont été évaluées par rapport aux données de fistulographie postopératoire. Une fuite biliaire s'est développée chez 17 patients (5.4%). Les facteurs de risque identifiés par analyse univariée ont été l'âge avancé, une grande surface sur la tranche de section (groupe de fuite biliaire vs. groupe sans fuite: 102.1 cm^2 vs. 66.4 cm^2, $p < 0.05$) et une exposition de la gaine Glissonienne dans la tranche de section (par ex. bisegmentectomie centrale, sous-segmentectomies 4 et 8). En regroupant les patients selon les résultats de leur fistulogramme postopératoire, ceux qui avaient eu un geste au niveau des voies biliaires proximales avaient une cicatrisation plus lente que ceux qui avaient une lésion distale. Le seul patient dont la fistulographie confirmait une atteinte biliaire périphérique avait une fuite intarissable et a nécessité une réintervention. Les hépatectomies dont la tranche de section est grande et/ou celles qui intéressent les gaines Glissoniennes sont à risque pour développer une fuite biliaire. Lorsque la fistulographie montre que les voies biliaires proximales ont été intéressées, il faut envisage un drainage nasobiliaire endoscopique; lorsque la fistulographie montre que les voies biliaires distales sont intéressées, il faut réopérer.

Resumen. El propósito del estudio fue identificar los factores de riesgo de escape biliar postoperatorio luego de una resección hepática y proponer estrategias terapéuticas para su manejo. En el período 1992–2000 se realizaron 313 resecciones hepáticas sin anastomosis coledocoyeyunal en nuestro instituto. Los factores de riesgo de escape biliar fueron identificados mediante análisis multivariado y se evaluaron las estrategias en relación con los hallazgos en la fistulografía postoperatoria. El escape biliar postoperatorio ocurrió en 17 pacientes (5.4%). El análisis univariado identificó riesgos altos tales como edad avanzada, una superficie amplia de incisión (grupo de escape biliar vs. grupo libre de escape biliar: 102.1 cm^2 vs. 66.4 cm^2, $p < 0.05$) y exposición de la cápsula de Gleason en la superficie de corte (ej. bisegmentectomía central, subsegmentectomía S4, S8). Al agrupar los pacientes según la fistulografía postoperatoria se encontró que aquellos con afección del canal biliar proximal requirieron más tiempo para resolución del escape biliar que aquellos sin afección demostrable del canal biliar. El paciente en quien la fistulografía demostró afección periférica del conducto biliar presentó un escape incontrolable y requirió reoperación. Las hepatectomías con una amplia superficie de sección y/o que resultan en exposición de la cápsula de Gleason presentan serios factores de riesgo de escape biliar. Cuando la fistulografía demuestra afección del canal biliar proximal, se requiere drenaje endoscópico por tubo nasobiliar; cuando la fistulografía demuestra afección periférica del canal biliar, se requiere reoperación.

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