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Is bile leakage after hepatic resection associated with impaired long-term survival?

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ABSTRACT

Background: Bile leakage (BL) is a frequent and severe complication following liver surgery. The aim of this study was to evaluate risk factors for BL, related other complications and association with long-term survival.

Methods: This study included all patients undergoing hepatectomy in a single centre from 2005 to 2016. Perioperative risk factors related to BL were identified using univariable and multivariable analysis. Kaplan-Meier method was used for survival analysis.

Results: BL occurred in 48 of 458 patients (11%). BLs were more frequent in patients after major hepatectomy ($p = 0.001$). Portal vein embolization, bilioenteric-anastomosis, lymphadenectomy, vascular reconstruction and operative time were significant factors for developing BL. Comparing patients with or without BL, BL was more commonly associated with other postoperative complications ($p = 0.001$), especially acute kidney failure and surgical-site-infections. There was no difference in 90-day-mortality ($p = 0.124$). The median disease-free survival was comparable (17 vs. 15 months, $p = 0.976$), also no difference was observed when stratifying for different tumour entities. There was no difference in median overall survival (OS) among malignant disease (35 vs. 47 months, $p = 0.200$) and in 3-year OS (46% vs. 59%). Multivariate analysis confirmed that postoperative liver failure and major hepatectomy were risk factors for reduced OS ($p = 0.010$).

Conclusions: Many concerns have been raised regarding tumour progression after major complications. In this study, we only found a relevant influence of BL on OS in pCC, whereas no association was seen in other cancer types, indicating that tumour progression might be triggered by BL in cancer types arising from the bile ducts itself.

Introduction

Hepatic resection (HR) is the primary therapy for benign and malignant liver tumours with potential for cure. Although liver surgery has undergone an impressive development, perioperative management is still challenging. Despite technical advances and high-experience in specialized centres, it is still burdened by a relevant rate of postoperative morbidity (4–48%) and mortality (0–10%) [1–15]. Common post-hepatectomy complications include fever, pleural effusion, subphrenic infection, haemorrhage, bile leakage (BL) and postoperative liver failure (POLF) [8,16–26]. BL represents a frequent and potentially severe complication after liver resection leading to prolonged hospital stay, delayed removal of abdominal drains and need for additional diagnostics and interventions [11,27–29].

Abbreviations: HR, hepatic resection; BL, bile leakage; POLF, postoperative liver failure; ISGLS, International Study Group of Liver Surgery; RFA, radiofrequency ablation; MWA, microwave ablation; OS, overall survival; SSI, surgical site infection; DFS, disease-free survival; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; pCC, perihilar cholangiocarcinoma; CRLM, colorectal liver metastasis; PVE, portal vein embolization.

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Previous studies have shown an incidence of BL between 3.6% and 7.4% [3,30–32]. After developing a standardized classification for BL by the International Study Group of Liver Surgery (ISGLS) in 2011, studies on BL were better comparable. Due to the effect of standardization, BL rates after HR considerably increased up to 35% in recent articles [6,7,33].

Besides its severe impact on perioperative outcome, data on the effect on long-term (oncological) outcome are still lacking. Especially in times of arising new minimal invasive therapies in interventional oncology like radiofrequency or microwave ablation (RFA, MWA), the role and safety of HR has to stand comparison to these possibly less invasive techniques. For example, RFA displays promising survival rates in selected patients with primary and secondary liver tumours (11–34 months median overall survival (OS)) with low morbidity (2–9%), low mortality (<1%) and lower costs for the health care system [34–37]. Hence, it is of crucial importance to know the potential impact of BL, as a specific surgical complication, on oncological outcome. The aims of this study were to clarify risk factors for postoperative BL and determine a possible association with other postoperative complications and long-term outcome.

Materials and methods

Patient selection

The clinical records of all patients undergoing HR with curative intent between 2005 and 2016 at the Department of Visceral, Transplant and Thoracic Surgery at the Medical University of Innsbruck (n = 458) were reviewed from a prospectively maintained database. The study protocol was approved by the Ethical Review Board committee of Medical University Innsbruck (EC number 1076/2017). Diagnosis for HR included primary hepatobiliary cancer, secondary metastatic tumour and benign lesions including hepatic adenoma, focal nodular hyperplasia, haemangioma and echinococcus disease. Except echinococcus disease all benign indications are consecutively summarized as “other benign lesions”.

Operative procedures

Major hepatectomy was defined as a resection of 3 or more segments. In most procedures an ultrasonic surgical aspirator (SONOCA; Söring, Quickborn, Germany) or crush-clamping technique with diathermia or bipolar coagulation was used, combined with selective clip application or ligature of vessels and bile ducts. Glissonian approach, total or selective intermittent occlusion of the vascular inflow and treatment of the liver raw surface with bipolar forceps and fibrin coated sealants was performed according to the surgeons’ preference. [38,39] Crush clamp was only used by one surgeon (exact data not available). In case of visible bile leakage at the resection site, small BLs were repaired by Z-suturing using 4–0 or 5–0 PDS (Ethicon, USA). In some cases, in order to avoid leakage of the bilioenteric reconstruction, a T-tube was used to support the bile duct or bilioenteric reconstruction. Abdominal drainages were routinely applied until 03/2016 and individually thereafter.

Definition of bile leakage

BL is clinically classified according to the ISGLS definition. Fluid collection detected on ultrasonography or computed tomography was also defined as BL when the leakage was either confirmed after further surgical exploration or percutaneous drainage. Patients were classified into the following two groups: patients with BL and patients without BL within 90 days after surgery. The BL group was further subdivided into grade A-C according to the ISGLS classification [33].

Postoperative complications and death

In general, complications were defined as adverse events resulting in deviation from the normal postoperative course within 90 days after HR. Sub-analysis of specific post-hepatectomy complications included POLF, acute kidney failure, haemorrhage, surgical site infection (SSI) and postoperative death within 90 days. Acute kidney failure was defined as necessity for postoperative haemodialysis in non-dialytic patients. POLF was defined according to the ISGLS definition [40]. The severity of complications was assessed using the Clavien-Dindo classification, graded 1 to 5 [41]. Major complications were defined as grade 3a or higher, thereby including all patients requiring endoscopic, radiologic or surgical intervention or intensive care treatment. Perioperative mortality was defined as death within 90 days after HR.

Treatment outcome

All patients were followed up for recurrence by clinical assessment and tumour markers every 3 months and computed tomography every 6 months. Further work up with magnetic resonance imaging or Positron Emission Tomography was performed additionally if required. Surgical and oncological outcomes were evaluated based on our prospectively maintained database and patients' clinical files; the last date of follow-up included was the 8th of January 2018. OS data were cross-checked with the official, national registry on mortality maintained by Statistics Austria [42].

Statistical analysis

Nominal variables are reported as frequencies and percentages and continuous variables as medians with either interquartile range or total range, respectively. Differences in continuous clinicopathological variables between patients with and without BL were analysed by the Wilcoxon signed-rank test, and differences in nominal variables were investigated by chi-square or Fisher's exact test. The predictors of BL were determined by univariable analyses. The probability for disease-free survival (DFS) was estimated by the Kaplan-Meier method and the results were compared by log-rank tests among patients with malignancy. For the investigation of OS all patients were included. P-values less than 0.05 were considered as significant and confidence intervals are reported on a 95% level. Data analysis was performed using SPSS 24.0 (IBM Inc., USA).

Results

Patients and surgical characteristics

Totally 458 patients were included in the study with a median age of 61 years (range 10–82). Demographic and clinical variables grouped by occurrence of bile leakage are summarized in Table 1.

A detailed information on the type of anatomical resection, according to the Brisbane 2000 Terminology [43] is depicted in Table 2. The majority of patients underwent major hepatectomy (52.7%) for malignancy (82.1%). Pathological diagnosis included hepatocellular carcinoma (HCC) in 49 cases, intrahepatic cholangiocarcinoma (ICC) in 39 cases, perihilar cholangiocarcinoma (pCC) in 55 patients, colorectal liver metastasis (CRLM) in 149 patients, non-colorectal metastatic liver tumours in 84 cases, hydatid disease in 35 patients and other benign liver disease in 48 cases. The median diameter of the largest lesion was 50 mm (mm; range 5–300), the median number of lesions was 2 (1–25), a bilobar

Table 1
Patient and tumour characteristics stratified by bile leakage; CI confidence interval; BMI body mass index; kg kilogramme; m metre; mm millimetre.

	Bile leak (n = 48)	No bile leak (n = 410)	P value
Age, median (range)	63 (28–78)	60 (10–82)	0.162
Female sex, n (%)	18 (37.5)	203 (49.4)	0.119
Cirrhosis, n (%)	2 (4.2)	24 (5.8)	1.000
Cardiac comorbidity, n (%)	11 (22.9)	57 (13.9)	0.129
Pulmonary comorbidity, n (%)	2 (4.2)	23 (5.6)	1.000
Diabetes, n (%)	9 (18.8)	43 (10.5)	0.094
Obesity (BMI>30 kg/m^2), n (%)	9 (18.8)	43 (10.5)	0.094
Neoadjuvant chemotherapy, n (%)	7 (14.6)	99 (24.1)	0.152
Bilobar involvement, n (%)	10 (22.7)	122 (32.0)	0.232
Synchronous disease, n (%)	10 (76.9)	131 (61.5)	0.380
Diameter of largest lesion, mm, median (range)	50 (5–270)	49 (6–300)	0.891

Table 2
Diagnosis and types of hepatectomy related to the incidence of bile leakage; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; pCC perihilar cholangiocarcinoma; CRLM colorectal liver metastases; ALPPS Associating liver partition and portal vein ligation.

	All	Bile leak	
	n	n	%
Malignant neoplasia	376	43	11.4
HCC	49	4	8.2
ICC	39	7	17.9
pCC	55	17	31.5
CRLM	149	9	6.0
Other secondary liver malignancies	84	6	7.1
Benign lesions	83	5	6.0
Echinococcus disease	35	4	11.4
Other benign liver lesions	48	1	2.1
Right hepatectomy	73	6	8.2
Left hepatectomy	29	9	31.0
Extended right hepatectomy	70	14	20.0
Extended left hepatectomy	12	3	25.0
Left lateral sectorectomy	37	1	2.7
Segmentectomy	25	2	8.0
Bisegmentectomy	14	2	14.3
ALPPS	1	1	100.0

involvement was found in 31.1% of cases. Surgical procedures included 197 anatomical resections (42.9%), 198 non-anatomical resections (43.1%) and a combined approach in 64 cases (13.9%). Laparoscopic resection was performed in 28 cases (6.1%). Operative data and postoperative complications are shown in Table 3.

Risk factors for BL

BL occurred in 48 of 458 patients (10.5%). According to the grading of the ISGLS classification [33], grade C BLs were most common (52.0%), followed by grade B (47.9%) and grade A leaks (2.1%). Patient characteristics did not differ significantly between patients with or without BL (Table 1). The ratio of BL was 11.4% in malignant disease and 6.0% in benign disease, respectively ($p < 0.001$). Furthermore, no statistical differences among the different tumour entities could be identified. BL was most frequently seen in pCC patients usually requiring complex bilioenteric reconstruction, followed by ICC patients. The associations of tumour entity and type of resection with the rate of postoperative BL are shown in Table 2.

The proportion of BL was significantly higher in patients after major hepatectomy compared to minor hepatectomy ($p < 0.001$). The incidence of BL for anatomical vs. non-anatomical vs. combined procedures was 17.8%, 5.1% and 4.7%, respectively ($p < 0.001$). After

Table 3
Operative parameters and postoperative complications stratified by bile leakage; PVE portal vein embolization; ml millilitre; POLF postoperative liver failure; d days, SSI surgical site infection.

	Bile leak (n = 48)	No bile leak (n = 410)	P value
Surgical variables			
Major hepatectomy, n (%)	36 (75.0)	206 (50.1)	**< 0.001**
PVE, n (%)	10 (20.8)	27 (6.6)	**0.002**
Pringle manoeuvre, n (%)	1 (2.1)	15 (3.6)	0.579
Lymphadenectomy, n (%)	14 (29.2)	36 (8.8)	**< 0.001**
Bilioenteric reconstruction, n (%)	22 (45.8)	36 (9.0)	**< 0.001**
Vascular reconstruction, n (%)	5 (10.4)	8 (1.9)	**0.007**
Operative time, hours, median (range)	6.8 (1 .4–14.4)	4.5 (1.0–17.4)	**<0.001**
Red cell concentrate, 300 ml units, median (range)	1 (0–9)	0 (0–28)	0.525
Fresh frozen plasma, 250 ml units, median (range)	5 (0–18)	0 (0–45)	0.121
Intraoperative blood loss, ml, median (range)	400 (0–5740)	400 (0–21582)	0.813
Hospital stay, median (range)	32 (6–106)	11 (0–119)	**< 0.001**
Postoperative morbidity and mortality			
Any complication, n (%)	48 (100.0)	114 (27.8)	**< 0.001**
Clavien-Dindo classification			**< 0.001**
Grade 1/2, n (%)	1 (2.1)	34 (29.8)	
Grade 3/4/5, n (%)	47 (97.9)	80 (70.2)	
POLF, n (%)	3 (6.3)	12 (2.9)	0.200
Acute kidney failure, n (%)	6 (12.5)	9 (2.2)	**0.002**
Haemorrhage, n (%)	4 (8.3)	13 (3.2)	0.090
SSI, n (%)	7 (14.6)	14 (3.4)	**0.003**
Operative death (<90d), n (%)	4 (8.3)	15 (3.7)	0.124

excluding patients with bilioenteric reconstruction the rate of BL was similar in the anatomical resection group compared to the entire cohort (Supplement 1).

Operative factors, such as previous portal vein embolization (PVE), locoregional lymph node dissection, bilioenteric reconstruction, vascular reconstruction and longer operative time were significantly associated with a higher rate of BL (Table 3).

Complications associated with BL

Patients with BL were significantly more likely to show any other additional postoperative complication, especially acute kidney failure and severe SSIs with prolonged wound healing. BL was not associated with the development of POLF. Complications of HR are summarized in Table 3.

Disease-free and overall survival

Excluding patients with benign disease, 376 patients with malignant disease were analysed for DFS. A total of 256 patients (68.1%) developed tumour recurrence. BL was not associated with recurrence (BL: 60.9%, no BL: 62.3%, $p = 0.873$).

The median DFS was 15 months (95%CI: 12.8–17.6). Regarding association of DFS and BL, the 1-, 3-, and 5-year DFS rates were 67.0%, 25.7% and 7.7% for patients with BL and 57.3%, 27.4% and 20.2% for patients without BL, respectively ($p = 0.976$; Fig. 1A) Furthermore there was no significant difference in median DFS among the different tumour entities (Table 4).

According to the ISGLS classification, the median DFS for grade B and C BLs was 43 (95%CI: 0–91.3) and 17 months (95%CI: 9.8–24.0), respectively ($p = 0.203$). The 1-, 3- and 5-year DFS rates were 69.4%, 53.4%, 28.6% for grade B and 70.0%, 13.8%, 13.8% for grade C, respectively.

Median follow-up after HR was 32 months (range 0.1–149.0). The median OS for the entire cohort (benign and malignant disease) with and without BL was 36 months (95%CI 17.1–54.8) and 60 months (95%CI 50.7–69.3), respectively ($p = 0.190$, Fig. 1B). Considering OS rates for malignant disease, there was no statistical difference in median OS for patients with (35 months; 95%CI 18.7–51.1) and without BL (47 months; 95%CI 39.3–54.9; $p = 0.200$, Fig. 1C).

OS rates for the different malignancies are shown in Table 4. Patients with pCC had an inferior OS when suffering from BL of 15.7 months (95%CI 7.5–24.1) vs. 31.3 months (95%CI 12.8–49.9; $p = 0.048$).

Multivariable analysis of factors associated with DFS and OS

Multivariable survival analysis (Table 5) did not show a significant association of extent of hepatectomy, lymphadenectomy, PVE, POLF or BL with DFS after hepatectomy. In contrast, major hepatectomy, lymphadenectomy and POLF were significant risk factors for reduced OS. All included variables did not show multicollinearity.

Discussion

This single centre study focused on the identification of risk factors for BL after hepatectomy, and the impact of this clinically relevant complication on long-term outcome.

Relevant risk factors for BL were PVE, lymphadenectomy, bilioenteric reconstruction, vascular replacement, operative time and occurrence of other complications. BL was significantly associated with inferior OS in pCC patients, however no influence of BL on DFS and OS could be detected for the entire cohort and the other tumour entities.

Published data suggest that in general, postoperative complications indeed show a negative impact on DFS and OS in a variety of other malignant tumours, whereas the influence of BLs has so far not been investigated in current literature [44].

The incidence of BL after HR in our study (10.5%) was consistent with data from previous studies [32,45–48]. After stratifying BL according to the definitions proposed by the ISGLS [33], the rate of grade B and C BL in our study reached 47.9% and 50.0%, respectively. These numbers were higher than in other studies [6,33,49]. An explanation for this high rate of surgical treatment of BLs might be our department's policy in liver transplantation, in which BLs are re-operated immediately. Furthermore, our data included 52.7% major hepatectomies, hereby considerably differing from several other reports with markedly lower numbers of major resections. The rather high rate of major and complex resections can be explained by the strong interventional radiology group in our centre, using stereotactic multiprobe RFA treating over 200 liver patients a year resulting in a smaller number of patients treated with minor (laparoscopic) resection. Location and treatment of patients with grad C bile leakage is shown in supplement 2.

In our data, when comparing cases with and without BL, we could not identify differences among patient and tumour characteristics. Concordant to the study by Tanaka et al., e.g. underlying liver cirrhosis had no influence on developing BL [30]. In addition, neoadjuvant chemotherapy was also not associated with occurrence of BL. In contrast to our results, a recent study with 6859

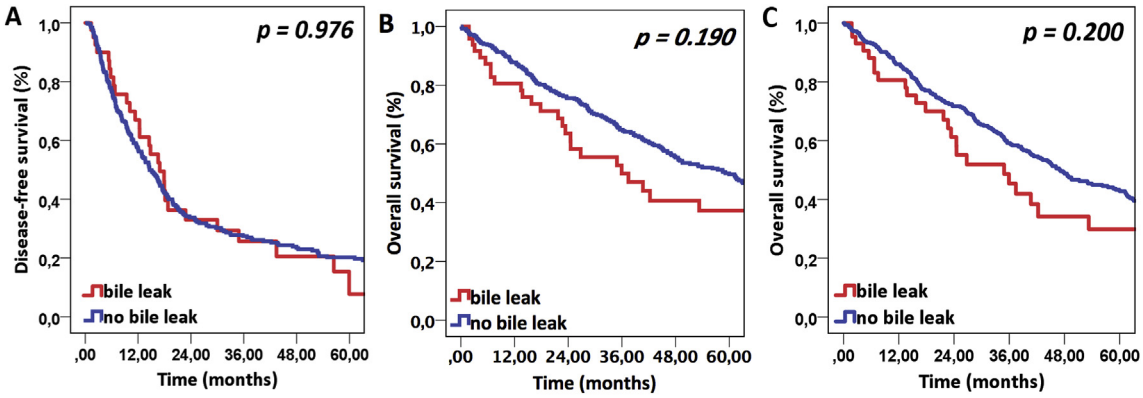

Fig. 1. Disease-free survival in patients with malignant disease (A), overall survival in all patients (B) and overall survival in patients with malignant disease (C), each stratified by bile leakage.

Table 4
Median DFS and OS for the different tumour entities stratified by bile leakage; n.c. non-calculable, due to low case numbers or survival probability was above 50%; CI confidence interval; HCC hepatocellular carcinoma; ICC intrahepatic cholangiocarcinoma; pCC perihilar cholangiocarcinoma; CRLM colorectal liver metastases.

	Bile leak (n = 48)	No bile leak (n = 410)	*P* value
DFS			
HCC (n = 49, months, 95% CI)	17.9 (0–53.3)	16.3 (9.5–23.1)	0.474
ICC (n = 39, months, 95% CI)	34.9 (8.1–61.7)	14.5 (8.5–20.5)	0.756
pCC (n = 55, months, 95% CI)	12.3 (10.6–14.1)	14.5 (10.6–18.3)	0.170
CRLM (n = 149, months, 95% CI)	43.4 (14.6–72.2)	15.6 (11.8–19.2)	0.133
Other extrahepatic malignancies (n = 74, months, 95%CI)	16.6 (1.3–31.9)	13.7 (6d.6–20.8)	0.470
OS			
HCC (n = 49, months, 95% CI)	42.3 (n.c.)	49.5 (24.6–74.5)	0.791
ICC (n = 39, months, 95% CI)	22.7 (2.2–43.2)	38.0 (25.5–50.5)	0.928
pCC (n = 55, months, 95% CI)	15.7 (7.5–24.1)	31.3 (12.8–49.9)	**0.048**
CRLM (n = 149, months, 95% CI)	n.c.	51.2 (41.0–61.5)	0.134
Other extrahepatic malignancies (n = 74, months, 95%CI)	35.9 (16.8–55.1)	61.5 (35.5–87.5)	0.519

Table 5
Multivariable analysis of factors associated with DFS and OS; HR hazard ratio; DFS disease-free survival; OS overall survival; CI confidence interval; PVE portal vein embolization; POLF postoperative liver failure.

Variable	HR (95% CI)	P value
DFS		
Major hepatectomy	1.3 (1.0–1.6)	0.090
Lymphadenectomy	1.1 (0.7–1.5)	0.793
PVE	0.7 (0.5–1.2)	0.213
POLF	2.8 (0.7–11.6)	0.159
Bile leakage	0.9 (0.6–1.4)	0.747
OS		
Major hepatectomy	1.4 (1.1–1.9)	**0.010**
Lymphadenectomy	1.6 (1.1–2.4)	**0.017**
PVE	1.0 (0.6–1.6)	0.982
POLF	13.7 (7.7–24.4)	**0.001**
Bile leakage	1.0 (0.7–1.6)	0.874

patients found that neoadjuvant chemotherapy was associated with postoperative BL [47].

We could not find a statistically significant difference in the incidence of BL between benign (6.0%) and malignant disease (11.4%). Comparable results were also found by Yamashita and colleagues published 2001, with 781 patients and a proportion of BL of 2.9% vs. 4.1% [31]. In contrast, malignant indication was found to be a risk factor for postoperative BL by Martin et al. [47].

When analysing occurrence of BL between different tumour entities, the highest rates of BL were detected in pCC (30.9%) and ICC (17.9%) patients. This may be caused by more extensive resections and biliary reconstructions [30,50]. While bilioenteric anastomoses are often not analysed in other papers, we decided to include them to correctly assess BL effects on oncological outcomes.

The rate of BL after major hepatectomy was three times higher compared to minor hepatectomy. Comparable results are found in the literature [31,47]. Anatomical resections, especially left hepatectomy, extended left hepatectomy and extended right hepatectomy had a high proportion of BL. This was coincident with the experience of other researchers [6,30–32,45,51]. and might be explained by challenges of correctly identifying bile ducts draining the caudate lobe or the right posterior segments that frequently drain into the left duct [52,53]. Anatomical resections can also be performed safely by experienced laparoscopic surgeons, although our centre has no extensive experience in laparoscopic major hepatectomies [54].

Previously established perioperative risk factors such as PVE, regional lymphadenectomy, bilioenteric reconstruction, vascular replacement and long operative time were all associated with BL. Huiskens et al. analysed the influence of PVE prior to liver resection. Patients experienced significantly more major complications in the PVE group, however the specific impact on BL was not analysed [55]. Another study showed no impact of PVE and lymph node dissection on the occurrence of BL [30].

Recent data from Zheng and colleagues suggested that bilioenteric anastomosis itself has the risk of anastomotic leakage, so the incidence of BL increased up to 50% [49]. Martin et al. found similar results [47].

In accordance to different previous studies our results confirmed, that a longer operative time correlates with a higher risk of biliary complications [31,45,47,56]. The cut off value defining longer operation time in these studies varies between a median >225 and > 300 min. Intraoperative blood loss and perioperative blood transfusion were not associated with BL in our study [31,32,45,57,58]. In summary, these results indicate that greater complexity of liver surgery leads to increased risk of biliary complications [4,58].

Additionally, patients with BL were more likely to experience other complications. Detailed analysis of postoperative morbidity revealed that acute kidney failure, postoperative haemorrhage and SSIs were independently associated with BL. Patients with BL were also more likely to experience severe complications (Clavien-Dindo grade 3/4). This could also be shown by Martin and colleagues [47] and might reflect the high complexity of this type of surgery.

Effects of BL on oncological outcome

Postoperative complications adversely affect long-term survival in certain cancer patients, such as oesophageal, pancreatic, colorectal and breast cancer [59–65]. While the long-term oncologic effects of postoperative complications have previously been evaluated in a number of studies, liver-specific complications such as BL after hepatic resection so far remained indeterminate. In two recent studies overall postoperative complications were independent predictors of OS and DFS after curative hepatectomy in patients with HCC [66,67]. Similar results were found by other authors [9,59,68,69]. Furthermore, an adverse impact of morbidity on survival was also reported in the field of CRLM. Patients with major complications had shorter survival than those with minor complications [70,71].

All of these studies analysed the influence of overall complications after hepatectomy and stratified by major complication according to the Clavien-Dindo classification (grade 3/4). To our knowledge our study provides the first data on the specific influence of BL on long-term survival as well as on the impact on tumour recurrence. In our cohort with different tumour entities, BL did not adversely affect DFS and OS, except in pCC. Despite the high rate of postoperative morbidity (4–48%) and mortality (0–10%) [1–15],

the oncological outcome seems unaffected by this complication. Another two recently published studies on ICC patients demonstrated that severe morbidity has a negative impact on OS and time to recurrence following HR [72,73].

The multivariable analysis showed that major hepatectomy, lymphadenectomy and POLF in contrast to BL were independent risk factors for an inferior OS. Doussot et al. found major hepatectomy as an independent predictor of severe morbidity in ICC patients, which leads to an adversely affected survival [72]. Furthermore Iguchi et al. recorded inferior survival results in cases with POLF [74]. On the contrary other authors reported, that postoperative complications were risk factors for OS but not recurrence-free survival [59,75–77]. Pravisani et al. revealed POLF and infected bilioma as prognostically negative factors [78]. These findings lead to the conclusion that surgery-related liver complications might be important activators for tumour recurrence. The possible underlying pathogenetic mechanisms are metabolic damage, infection and inflammation, which are mediated by changes in chemo- and cytokine profiles [66,74,77,79,80]. Besides inducing suppression of the cell-mediated immunity and natural-killer cell function, these changes are associated with a direct oncogenic effect, stimulating circulating tumour cell adhesion and enhancing neo-angiogenesis [66,77,79,80]. As a result residual tumour cells survive in the host and promote growth of metastasis [59,66,67,74,77,79].

However it is still unclear whether immunological suppression due to postoperative complications leads to proliferation of residual cancer cells or, alternatively, if patients with a more aggressive tumour have a higher tendency for postoperative complications [59]. In the present study we identified mainly surgery-related risk factors rather than tumour-related ones as relevant determinants for complications. These findings are in line with other reports [59,66,77,81,82].

Additionally to the retrospective design of the study, the rather small size of the study population suffering from BL, the heterogeneity of tumour entities and the lack of details on specific cause of patient's death should be considered as limitations.

In conclusion, many concerns have been raised regarding tumour progression after major complications, but no explicit analysis of BL on survival has been demonstrated. In this study, we only found a relevant influence of BL on OS in pCC, whereas no influence was seen in other cancer types, indicating that tumour progression might be triggered by BL only in cancer types arising from the bile ducts themselves.

Conflict of interest statement

All authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.02.021.

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