ORIGINAL ARTICLE

Surgical outcomes of laparoscopic and open resection of benign liver tumours in the Netherlands: a nationwide analysis

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Abstract

Background: Data on surgical outcomes of laparoscopic liver resection (LLR) versus open liver resection (OLR) of benign liver tumour (BLT) are scarce. This study aimed to provide a nationwide overview of postoperative outcomes after LLR and OLR of BLT.

Methods: This was a nationwide retrospective study including all patients who underwent liver resection for hepatocellular adenoma, haemangioma and focal nodular hyperplasia in the Netherlands from 2014 to 2019. Propensity score matching (PSM) was applied to compare 30-day overall and major morbidity and 30-day mortality after OLR and LLR.

Results: In total, 415 patients underwent BLT resection of whom 230 (55.4%) underwent LLR. PSM for OLR and LLR resulted in 250 matched patients. Median (IQR) length of stay was shorter after LLR than OLR (4 versus 6 days, 5.0–8.0, $p < 0.001$). Postoperative 30-day overall morbidity was lower after LLR than OLR (12.0% vs. 22.4%, $p = 0.043$). LLR was associated with reduced 30-day overall morbidity in multivariable analysis (aOR:0.46, CI:0.22–0.95, $p = 0.043$). Both 30-day major morbidity and 30-day mortality were not different.

Conclusions: LLR for BLT is associated with shorter hospital stay and reduced overall morbidity and is preferred if technically feasible.

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Introduction

The role of liver resection in the treatment of benign liver tumours (BLT) remains challenging.[1,2] Indications for resection differ per tumour type as clinical implications across BLT (sub) types vary significantly.[2] The majority of BLT are comprised of hepatocellular adenoma (HCA), haemangioma, and focal nodular hyperplasia (FNH).[3] The majority of these tumours occurs mainly in middle-aged women and are most accurately radiologically characterized through hepatobiliary contrast enhanced magnetic resonance imaging (CE-MRI).[4]

HCAs are associated with long term oral contraceptive pill use and obesity.[5,6] Tumours of ≥50 mm diameter are associated with haemorrhage (15–20%) and malignant transformation to hepatocellular carcinoma has been described.[7,8] Conservative treatment, by estrogen lowering life style advices including oral contraceptive pill cessation and weight loss, can lead to HCA regression.[9,10] Current European guidelines recommend a wait-and-see period of six months after commencing life style advices. Current guidelines advocate surgery if tumour size remains ≥50 mm^2. This period, though, may be too short for large HCAs to regress to sub-50mm size.[11]

Indications for resection in FNH or hemangioma are less distinct, as risk of hemorrhage in haemangiomas and FNHs is very rare in the former, and non-existent in the latter.[12,13] However, both hemangioma and FNHs are known to cause abdominal complaints such as pain, nausea or bloatedness by compression.[14] A rare complication associated with large haemangiomas (≥50 mm) is Kasabach-Merritt syndrome - a consumptive coagulopathy.[15] These consequences could warrant surgical intervention in selected patients as the FNH or hemangioma burden could outweigh the risk of adverse events associated with liver resection.[2]

As indications for BLT surgery are ambiguous, therapeutic strategies are often drafted through shared decision making by patient and clinician. This process necessitates availability of accurate and elaborate information with regards to surgical outcomes as surgical burden should outweigh risks of post-operative morbidity. Up to now limited series on outcomes after surgery for benign liver tumors have been performed and evidence is scarce. Additionally, potential strategies to decrease adverse events remain controversial.[16–19] As for malignant tumours, laparoscopic liver resection (LLR) may have potential benefits over open liver resection (OLR) by decreasing blood loss, length of hospital stay (LOS), and postoperative morbidity.[16,20,21] However, the role of laparoscopy in BLT surgery has been scientifically underexposed too.

The current study aimed to provide an evaluation of post-operative surgical outcomes after liver resection for BLT, to assess laparoscopy influence on postoperative outcomes, and to identify predisposing factors for post-operative complications using a multivariable analysis in a nationwide, population-based design.

Methods

A nationwide population-based study was performed in the Netherlands. Data were retrieved from the Dutch Hepato Biliary Audit (DHBA), a nationwide registry in which all Dutch hospitals eligible for liver surgery are obliged to record all liver resections performed. Data verification was performed by a trusted third-party to provide insight into DHBA data completeness and quality.[22] No ethical approval to perform this study was needed under Dutch law as the DHBA is part of the Dutch inspectorate of health care and research is carried out with an anonymized dataset.

Patient selection

Included were patients who underwent liver resection for HCA, haemangioma or FNH in the Netherlands between the 1st of January 2014 and December 31st 2019 and were registered in the DHBA before the 1st of April 2020. Patients were excluded if information regarding date of birth, date of surgery, or type of intervention was missing. Patients who underwent liver resection for unspecified type of BLT were excluded.

Definitions and outcomes

Major liver resection was defined as resection of three or more adjacent segments as per Couinaud classification.[23] Outcomes were stratified for type of BLT and for surgical approach. Surgical approach was categorized for OLR and LLR, converted procedures were included as LLR in the intention to treat analysis.

Postoperative outcomes included 30-day overall morbidity (i.e. any complication within 30-days of surgery), and LOS calculated as time between date of surgery and the date of discharge. Furthermore, 30-day major morbidity, defined as a Clavien-Dindo grade IIIa or higher complication (i.e. requiring re-intervention, medium care or intensive care management or death) within 30 days of surgery, and 30-day mortality defined as death within 30 days of surgery or during initial hospitalization were assessed.[24]

Other postoperative outcomes included specific complication rates such as bile leakage, postoperative hemorrhage requiring reintervention, postoperative liver failure according the International Study Group of Liver Surgery, deep surgical site infection (i.e biloma or abscess), incisional surgical site infection, pneumonia, myocardial complication or a thrombo-embolic complication.[25]

Variables

Patient characteristics included age, sex, American Society of Anesthesiologists (ASA) classification, comorbidity score according the Charlson Comorbidity Index (CCI), history of liver disease and a history of liver resection. Tumour characteristics included type of BLT, number of BLT and diameter of largest BLT prior to treatment. Treatment characteristics included surgical approach, extensiveness of liver resection (major or minor), and type of hospital (i.e. tertiary referral hospital or regional hospital) where treatment took place.

Statistical analysis

Baseline characteristics and postoperative outcomes were compared between groups using the Chi-square test or Fisher exact test as appropriate for categorical variables. The independent two-sample t-test was used for continuous outcomes which were presented as medians with interquartile ranges (IQR).

Table 1 Baseline characteristics for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach

Factor	Open Liver Resection	Laparoscopic Liver Resection	p-value
	N (%)	N (%)	
Total	185	220	
Patient characteristics			
Sex			0.371
Male	18 (10)	30 (13)	
Female	167 (90)	200 (87)	
Age in years			0.101
<50	118 (64)	160 (70)	
50–64	51 (28)	42 (18)	
65–79	16 (9)	27 (12)	
≥80	0 (0)	1 (0)	
Charlson Comorbidity Index (CCI)			0.543
0/1	156 (84)	200 (87)	
2 +	29 (16)	30 (13)	
Body Mass Index (BMI)			0.723
Mean (sd)	27.5 (5.7)	27.3 (6.0)	
American Society of Anesthesiology (ASA) classification			0.097
ASA I/II	168 (92)	198 (86)	
ASA III+	15 (8)	32 (14)	
Missing	2	0	
History of liver resection			**0.017**
No	172 (97)	228 (100)	
Yes	6 (3)	0 (0)	
Missing	7	2	
History of liver disease[a]			0.728
No	177 (97)	220 (98)	
Yes	6 (3)	5 (2)	
Missing	2	5	
Histopathological liver disease			
Normal liver	121 (70)	140 (68)	0.362
Steatosis	36 (21)	55 (27)	
Steato-hepatitis	7 (4)	7 (3)	
Cirrhosis	3 (2)	3 (1)	
Sinusoidal dilatation	6 (3)	2 (1)	
Missing	12	23	
Tumor- and operative characteristics			
Number of BLT			0.835
1	119 (73)	161 (75)	
2	17 (10)	17 (8)	
3	9 (6)	14 (7)	
≥4	18 (11)	23 (10)	
Missing	22	15	
Maximum diameter of largest BLT (mm[b])			0.770
<50	40 (27)	56 (29)	

Table 1 (*continued*)

Factor	Open Liver Resection	Laparoscopic Liver Resection	p-value
	N (%)	N (%)	
≥50	109 (73)	138 (71)	
Missing	36	36	
Bilobar disease			**0.011**
No	107 (58)	161 (71)	
Yes	77 (42)	67 (29)	
Missing	1	2	
Major liver resection			**<0.001**
No	117 (63)	208 (90)	
Yes	68 (37)	22 (10)	
Type of BLT			0.513
Hepatocellular adenoma	114 (62)	131 (57)	
Haemangioma	38 (21)	48 (21)	
Focal nodular hyperplasia	33 (18)	51 (22)	
Type of hospital[c]			0.223
Regional hospital	50 (27)	76 (33)	
Tertiary referral hospital	135 (73)	154 (67)	

Bold p-values indicate statistical significance of $p < 0.05$.
[a] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[b] Millimeter.
[c] Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery.

Funnel plots were plotted for evaluation of hospitals performance relative to mean outcome rates in the Netherlands to address hospital variation concerning 30-day overall and major morbidity after resection.

Univariable and multivariable logistic regression was performed to assess risk factors for adverse events in the complete population. The association of risk factors with adverse events were reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Variables were entered into multivariable analysis after univariable testing with the outcome as dependent variable. Variables were included in multivariable analysis if $p < 0.20$ after univariable analysis. Statistical significance was defined as a two-sided $p < 0.05$ in the multivariable model. To assess the influence of annual overall and BLT resection volume on postoperative outcomes in the complete BLT population, both variables were included in these logistic regression models. Annual overall volume and BLT resection volume were calculated as total number of liver resections and BLT indicated liver resections performed per hospital per year, respectively. Overall volume was categorized for <20, 20–39, 40–59, 60–79, and ≥80 procedures, with the first two categories merged for analysis due two low inclusions. Annual hospital volume for BLT resection was categorized <5, 5–15, and ≥15 procedures.

Multicollinearity was assessed in all logistic regression models, and indicated if the calculated variance inflation factor was higher than 2.5.

Differences in postoperative outcomes between OLR and LLR were assessed after propensity score matching (PSM). As a first step in PSM, a multivariable logistic regression was used to estimate propensity scores per patient. Hereafter, PSM was performed with a 1:1 ratio using the nearest neighbor method with a caliper of 0.01. Covariates for PSM were, ASA score, type of BLT, history of liver resection, number of BLT, diameter of largest BLT, bilobar disease, and major liver resection. In order to assess the quality of the matching process standardized mean differences (smd) were used. Standard mean differences below 0.1 for baseline characteristics between the two groups indicate negligible differences between the OLR and LLR groups after PSM. Differences in tumour and operative techniques needed to be negligible in order to decrease possible selection bias. After PSM, baseline characteristics and outcomes were compared between the groups using the Chi-square test or Fisher exact test for categorical variables. Continuous outcomes were presented as medians with interquartile ranges (IQR). A multivariable logistic regression model was performed using backward selection to identify which variables were associated with 30-day overall

Table 2a Univariable and multivariable logistic regression model to assess the association of patient-, tumor- and surgical characteristics with 30-day overall morbidity after benign liver tumour (BLT) resection in the Netherlands between 2014 and 2019

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.556			
Male	48	1					
Female	367	1.29	0.59–3.25				
Age (years)				0.080			**0.016**
≤65	371	1			1		
>65	44	1.90	0.90–3.81		2.65	1.17–5.80	
Missing[a]							
Charlson Comorbidity Index (CCI)				0.340			
0/1	356	1					
2+	59	1.39	0.68–2.67				
Body Mass Index				0.569			
Mean (sd)		0.99	0.94–1.03				
American Society of Anesthesiology (ASA) classification				0.742			
I/II	366	1					
III +	47	1.14	0.50–2.38				
Missing[b]	2						
History of liver disease[b]				0.020			**0.037**
No	397	1			1		
Yes	11	4.26	1.20–14.5		4.20	1.01–16.0	
Missing[b]	7						
Histopathological liver disease[d]				0.344			
No	261	1					
Yes	119	1.18	0.66–2.07	0.563			
Missing	35	1.88	0.78–4.19	0.137			
Number of BLT				0.808			
1	280	1					
2	34	0.83	0.27–2.09	0.720			
3	23	0.73	0.17–2.22	0.615			
≥4	41	1.36	0.58–2.93	0.453			
Missing	37	1.38	0.56–3.09	0.454			
Maximum diameter largest BLT (mm)[b]				0.287			
<50	96	1					
≥50	247	0.74	0.40–1.40	0.342			
Missing	72	1.58	0.76–3.32	0.220			
Bilobar disease				0.195			0.160
No	268	1			1		
Yes	144	1.41	0.83–2.36		1.48	0.85–2.57	
Missing[b]	3						
Type of benign liver tumour				0.841			0.951
Hepatocellular adenoma	245	1			1		
Haemangioma	86	1.18	0.62–2.19	0.595	1.04	0.51–2.06	0.905
Focal nodular hyperplasia	84	0.96	0.48–1.83	0.909	1.12	0.53–2.25	0.753

Table 2a (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Major liver resection				0.005			**0.037**
No	325	1			1		
Yes	90	2.21	1.26–3.83		1.94	1.04–3.61	
Surgical approach				0.003			**0.044**
OLR	185	1			1		
LLR	230	0.46	0.27–0.77		0.55	0.41–0.98	
Type of hospital[c]				0.535			
Regional hospital	126	1					
Tertiary referral hospital	289	1.20	0.69–2.14				
Annual hospital volume of BLT resection				0.457			
<5	150	1					
5–15	163	1.14	0.62–2.09	0.678			
>15	102	1.51	0.79–2.89	0.215			
Overall annual hospital volume				0.827			
0–39	58	1					
40–59	31	0.57	0.15–1.82	0.366			
60–79	55	0.85	0.33–2.17	0.737			
>80	271	0.81	0.41–1.70	0.555			

Bold p-values indicate statistical significance of $p < 0.05$.
Mm = millimeter.
OLR: Open liver resection; LLR: Laparoscopic liver resection.
[a] Missing not included in analyses based on relatively small group.
[b] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[c] Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.
[d] All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

morbidity and 30-day major morbidity corrected for possible confounders in the PSM population.

All analyses were performed in R version 3.2.2® (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 415 patients were included of whom 246 (59.0%) underwent resection for HCA, 87 (20.7%) for haemangioma, and 85 (20.3%) for FNH. Laparoscopic resection was performed in 230 (55.4%) patients (Table 1).

Patients who underwent resection because of HCA or FNH were more often female, were younger, had lower CCI, and had lower ASA scores versus patients who underwent resection because of haemangioma (Supplementary Table 1). Resection of HCA was more frequently performed for a higher number of tumours, and for a larger tumour diameter compared to haemangioma or FNH, resulting in more frequent major liver resections. Likewise, resection of HCA was performed more often in tertiary referral centres.

The total number of BLT resection did not increase during the study period. Laparoscopic liver resection was performed more frequently over the years as 16 LLR were performed in 2014, 56 in 2018 and 29 in 2019 ($p < 0.001$). Laparoscopic resection was less often applied in case of bilobar disease or when a major liver resection was performed (Table 1).

Postoperative outcomes and hospital variation

After BLT resection, 30-day overall morbidity after BLT resection occurred in 73 patients (17.5%), and 30-day major morbidity occurred in 24 patients (5.7%). Thirty-day mortality did not occur (0%). Overall 30-day morbidity rates ranged from 8.3% to 50% between hospitals. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day overall morbidity rate compared to the mean 30-day overall morbidity (Supplementary Figure 1a). Six hospitals had a significantly lower 30-day overall morbidity compared to the mean 30-day overall morbidity. Major morbidity rates between hospitals ranged from 3.5% to 19.4%. None of the hospitals performing liver surgery for BLT had a significantly higher 30-day major morbidity rate compared to the mean 30-day major morbidity

Table 2b Univariable and multivariable logistic regression model to assess the association of patient and tumor characteristics with 30-day major morbidity after benign liver tumour (BLT) resection in the Netherlands between 2014 and 2019

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Sex				0.612			
Male	48	1					
Female	367	1.47	0.41–9.35				
Age (years)				0.756			
≤65	371	1					
>65	44	1.22	0.28–3.74				
Charlson Comorbidity Index (CCI)				0.127			**0.029**
0/1	356	1			1		
2+	59	2.213	0.74–5.33	0.315	3.20	1.06–8.81	
Body Mass Index		0.96	0.89–1.03				
American Society of Anesthesiology (ASA) classification				0.859			
I/II	366	1					
III +	47	1.12	0.26–3.42				
Missing[a]	2						
History of liver disease[b]				0.619			
No	397	1					
Yes	11	1.70	0.09–9.52				
Missing[a]	7						
Histopathological liver disease[d]				0.327			
No	261	1					
Yes	119	0.72	0.23–1.91	0.533			
Missing[a]	35	2.12	0.58–6.27	0.207			
Number of BLT				0.314			
1	280	1					
2	34	0.13	0.01–36.8	0.989			
3	23	0.61	0.04–3.45	0.694			
≥4	41	0.75	0.12–2.72	0.702			
Missing	37	1.28	0.29–4.05	0.700			
Maximum diameter largest BLT (mm)[a]				0.526			
<50	96	1					
≥50	247	1.38	0.48–4.97	0.577			
Missing	72	2.09	0.57–8.45	0.268			
Bilobar disease				0.864			
No	268	1					
Yes	144	0.92	0.37–2.16				
Missing[a]	3						
Type of benign liver tumour				0.236			0.099
Hepatocellular adenoma	245	1			1		
Haemangioma	86	0.71	0.15–2.06	0.502	0.61	0.13–2.01	0.457
Focal nodular hyperplasia	84	1.06	0.72–4.63	0.178	2.41	0.90–6.22	0.071
Major liver resection				0.018			**0.011**
No	325	1			1		

Table 2b (*continued*)

Factor	N	Univariable analysis			Multivariable analysis		
		OR	CI (95%)	P-value	aOR	CI (95%)	P-value
Yes	90	2.78	1.16–6.44		3.48	1.32–9.14	
Surgical approach				0.333			0.934
OLR	185	1					
LLR	230	0.66	0.29–1.52		0.96	0.39–2.41	
Type of hospital[c]				0.896			
Regional hospital	126	1					
Tertiary referral hospital	289	1.06	0.45–2.81				
Annual hospital volume of BLT resection				0.983			
<5	150	1					
5–15	163	0.92	0.35–2.41	0.856			
>15	102	0.98	0.32–2.80	0.969			
Overall annual hospital volume				0.269			
0–39	58	1					
40–59	31	1.57	0.36–6.41	0.526			
60–79	55	0.61	0.12–2.62	0.515			
>80	271	0.50	0.17–1.60	0.199			

Bold p-values indicate statistical significance of $p < 0.05$.
Mm = millimeter.
OLR: Open liver resection; LLR: Laparoscopic liver resection.
[a] Missing not included in analyses based on relatively small group.
[b] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[c] Type of hospital: tertiary referral centers are defined as hospitals with highest expertise on oncologic surgery.
[d] All patients with a nonnormal histological diagnosis of liver tissue are placed under 'Yes'.

rate (Supplementary Figure 1b). Five hospitals had a significantly lower 30-day major morbidity compared to the mean 30-day major morbidity.

Risk factors for adverse events and influence of hospital volume

In univariable logistic regression and multivariable logistic regression, several risk factors for adverse events were observed. Age above 65 (aOR 2.65, CI 1.17–5.80, p = 0.016), history of liver disease (aOR 4.20, CI 1.01–16.0, p = 0.037) and major liver resection (aOR 1.94, CI 1.04–3.61, p = 0.037) were independently associated with higher 30-day overall morbidity (Table 2a). Laparoscopic liver resection (aOR 0.55, CI 0.41–0.98, p = 0.044) was associated with lower 30-day overall morbidity. No influence of type of BLT or hospital volume was observed for 30-day overall morbidity.

Also, CCI higher than 2 (aOR 3.20, CI 1.06–8.81, p = 0.029) and major liver resection (aOR 3.48, CI 1.32–9.14, p = 0.011) were associated with higher 30-day major morbidity (Table 2b). No influence of surgical approach, type of BLT or hospital volume was observed for 30-day major morbidity.

Propensity score matching: baseline- and surgical characteristics

PSM was performed to minimize baseline differences in the OLR and LLR groups (Table 3). Matching resulted in balanced covariates as the standard mean difference was 0.100 or lower for all variables except for histological diagnosis as more patients with parenchymal liver disease were included in the LLR group. This minor imbalance proved insignificant as no significant differences in baseline characteristics were observed between both resection groups. For analysis of postoperative outcomes, 125 patients (50%) who underwent OLR and 125 patients (50%) who underwent LLR were included.

Postoperative outcomes

Median LOS was shorter after LLR compared to OLR (4 days (3–6) vs. 6 days (5–8), p < 0.001). Thirty-day overall morbidity occurred in 15 patients after LLR 12.0% which was lower compared to the 28 patients (22.4%, p = 0.043) in which a complication occurred after OLR (Fig. 1a). The 30-day major morbidity rate was not different between LLR and OLR. Six patients (4.8%) and 8 patients (6.4%)

Table 3 Baseline characteristics after propensity score matching for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection stratified for surgical approach

Factor	Open Liver Resection	Laparoscopic Liver Resection	p-value	smd
	N (%)	N (%)		
Total	125	125		
Patient characteristics				
Sex			0.570	0.096
Male	14 (11)	18 (14)		
Female	111 (89)	107 (86)		
Age in years			0.684	0.077
<65	113 (90)	110 (88)		
≥65	12 (10)	15 (12)		
Charlson Comorbidity Index (CCI)			0.487	0.098
0/1	102 (82)	109 (87)		
2 +	23 (18)	16 (13)		
Body Mass Index (BMI)			0.652	0.081
Mean (sd)	27.2 (6.0)	27.3 (5.6)		
American Society of Anesthesiology (ASA) classification			0.342	0.100
ASA I/II	115 (92)	109 (87)		
ASA III+	10 (8)	16 (13)		
History of liver resection			1.000	<0.001
No	124 (99)	124 (99)		
Yes	1 (1)	1 (1)		
Missing[c]	1	1		
History of liver disease[a]			1.000	0.045
No	121 (97)	119 (98)		
Yes	4 (3)	3 (99)		
Missing[c]	0	3		
Histopathological liver disease			0.342	0.104
Normal liver	83 (80)	73 (72)		
Abnormal liver parenchyma[b]	21 (20)	29 (28)		
Missing[c]	21	23		
Tumor- and operative characteristics				
Number of BLT			1.000	<0.001
≤3	102 (82)	102 (82)		
≥4	13 (18)	13 (18)		
Missing[c]	10	10		
Maximum diameter of largest BLT (mm[c])			0.911	0.035
<50	35 (32)	32 (30)		
≥50	75 (68)	74 (70)		
Missing[c]	15	19		
Bilobar disease			1.000	<0.001
No	81 (65)	81 (65)		
Yes	43 (34)	43 (34)		
Missing[c]	1	1		
Major liver resection			1.000	<0.001
No	105 (84)	105 (84)		

Table 3 (*continued*)

Factor	Open Liver Resection	Laparoscopic Liver Resection	p-value	smd
	N (%)	N (%)		
Yes	20 (16)	20 (16)		
Type of BLT			0.951	0.040
Hepatocellular adenoma	70 (56)	72 (58)		
Haemangioma	26 (21)	26 (21)		
Focal nodular hyperplasia	29 (23)	27 (22)		
Type of hospital[d]			0.893	0.034
Regional hospital	42 (34)	40 (32)		
Tertiary referral hospital	84 (66)	85 (68)		

Bold p-values indicate statistical significance of $p < 0.05$.
Smd = standard mean difference.
[a] History of liver disease containing liver cirrhosis, esophageal variceal disease, hepatorenal syndrome, liver failure, alcoholic liver disease, toxic liver disease (mild), (chronic) hepatitis or liver fibrosis.
[b] Abnormal liver parenchyma includes steatosis, sinusoidal dilatation, cirrhosis and steatohepatitis.
[c] millimeter.
[d] Type of hospital: tertiary referral center are defined as hospitals with highest expertise on oncologic surgery.

experienced 30-day major morbidity after LLR and OLR respectively ($p = 0.783$).

Postoperative outcomes stratified for LLR and OLR did not show differences in specific liver-related complication rates (Fig. 1b). Similarly, no differences were observed in other complication rates (i.e. pneumonia, cardiac, thrombo-embolic, or infectious) between LLR and OLR (data not shown).

Associated factors with 30-day overall morbidity and 30-day major morbidity after PSM

Multivariable logistic regression in the PSM population showed that bilobar disease (aOR 2.11, CI 1.04–4.28, $p = 0.037$) was associated with higher 30-day overall morbidity (Table 4). Performing LLR was independently associated with lower 30-day overall morbidity (aOR 0.46, CI 0.22–0.95, $p = 0.043$). No variables were independently associated with 30-day major morbidity.

Discussion

This population-based, propensity score matched, study comprises a nationwide study on surgical outcomes for BLT and encompasses one of the largest series up to date. Overall 30-day morbidity was 17.5%, and 30-day major morbidity was 5.7% without mortality. Minimal hospital variation for postoperative outcomes was present. Several hospitals demonstrated better than average performance. Risk factors for 30-day overall morbidity included age above 65, history of liver disease and major liver resection, while risk factors for 30-day major morbidity were CCI above 2 and major liver resection. No influence of hospital volume or type of BLT was observed. PSM was performed and resulted in 250 matched patients who underwent OLR and LLR. LLR proved beneficial with regards to postoperative outcomes such as LOS and 30-day overall morbidity. A more favourable outcome regarding 30-day overall morbidity was also observed for LLR after adjusting for confounding factors, as LLR was associated with lower 30-day overall morbidity. This could indicate that use of LLR may assist in postoperative morbidity reduction when performing BLT indicated liver resection.

Historically, limited series on surgical outcomes of BLT have been reported. Previous studies show overall morbidity rates of 10–20% and major morbidity rates around 10% after resection of BLT.[13,20,21,26–28] Previously reported surgical outcomes after BLT resection range 10–35% and 5–15% for overall and major morbidity, respectively. Hence, the current observations are concordant and indicate resection of haemangioma and FNH in the Netherlands to be comparable to earlier studies.[29–31]

Several risk factors were observed in all resected BLT patients for adverse events. Higher age, higher comorbidity scores and factors associated with the extent of the liver resection were associated with 30-day overall morbidity and 30-day major morbidity. These risk factors are comparable with earlier described risk factors in liver resection for malignant indications.[32,33] Hospital variation concerning postoperative outcomes of BLT resection is present in the Netherlands without any hospitals performing significantly worse than the nationwide average. Most BLT resections were performed in higher volume centres. Some high-volume centres performed better than average (no statistical significance). Overall annual hospital volume for all liver resections and annual hospital of BLT resection, though, were not correlated with postoperative outcomes, similar to prior observations.[34] This observation, alongside the aforementioned results equal

Table 4 Results of stepwise multivariable logistic regression model after propensity score matching for patients diagnosed with a benign liver tumour (BLT) between 2014 and 2019 in the Netherlands who underwent liver resection

30-day overall morbidity		**Multivariable analysis**		
Factor	**N**	**OR**	**CI (95%)**	**P-value**
Charlson Comorbidity Index (CCI)				0.786
0/1	211	1		
2 +	39	1.14	0.43–2.78	
American Society of Anesthesiology (ASA) classification				0.820
I/II	224	1		
III+	26	1.15	0.33–3.47	
Histopathological liver disease				0.911
Normal liver	156	1		
Abnormal liver parenchyma	50	1.19	0.51–2.74	0.684
Missing	44	1.16	0.29–3.74	0.817
Maximum diameter of largest BLT (mm)				0.240
<50	67	1		
≥50	149	0.58	0.25–1.35	0.197
Missing	34	1.23	0.42–3.44	0.691
Bilobair disease				**0.037**
No	162	1		
Yes	86	2.11	1.04–4.28	
Missing[a]	2			
Type of BLT				0.805
Hepatocellular adenoma	142	1		
Haemangioma	52	1.21	0.47–3.04	0.685
Focal nodular hyperplasia	56	0.85	0.32–2.11	0.727
Major liver resection				0.171
No	210	1		
Yes	40	1.85	0.74–4.38	
Surgical approach				**0.038**
OLR	125	1		
LLR	125	0.46	0.22–0.95	
30-day major morbidity		**Multivariable analysis**		
Factor	**N**	**OR**	**CI (95%)**	**P-value**
Charlson Comorbidity Index (CCI)				0.253
0/1	211	1		
2 +	39	3.44	0.85–12.1	
American Society of Anesthesiology (ASA) classification				0.072
I/II	224	1		
III+	26	2.48	0.45–10.6	
Histopathological liver disease				0.889
Normal liver	156	1		
Abnormal liver parenchyma	50	0.97	0.22–3.78	0.966
Missing	44	1.34	0.20–7.58	0.632
Type of BLT				0.275
Hepatocellular adenoma	142	1		
Haemangioma	52	0.53	0.07–2.73	0.488

Table 4 (*continued*)

30-day major morbidity		Multivariable analysis		
Factor	**N**	**OR**	**CI (95%)**	**P-value**
Focal nodular hyperplasia	56	2.10	0.55–7.70	0.259
Major liver resection				0.145
No	210	1		
Yes	40	2.72	0.68–9.37	
Surgical approach				0.600
OLR	125	1		
LLR	125	0.73	0.21–2.40	

Bold p-values indicate statistical significance of $p < 0.05$.
[a] Missing not included in analyses based on relatively small group.

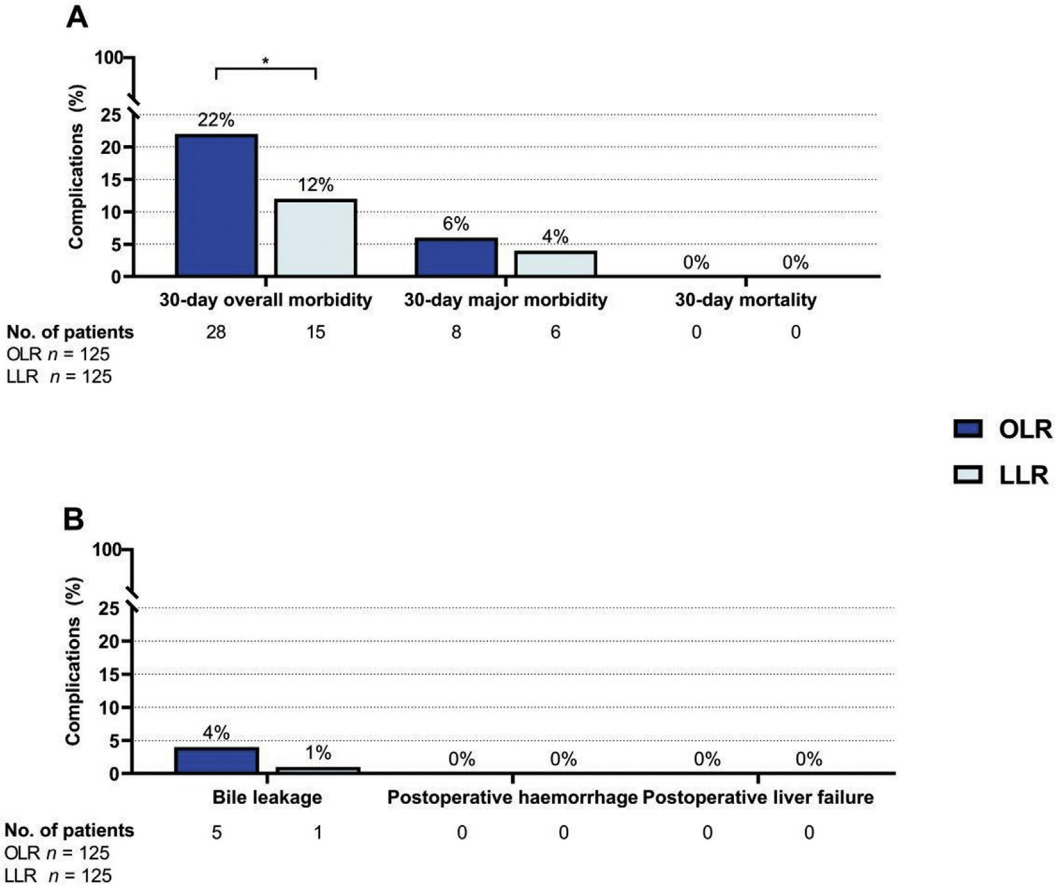

Figure. 1 a and b). Overview of percentage of patients included after propensity score matching with main outcomes and liver-specific outcomes after benign liver tumour resection in the Netherlands stratified for open liver resection (OLR) and laparoscopic liver resection (LLR). * Indicates $p < 0.05$, ** Indicates $p < 0.01$, *** Indicates $p < 0.001$, P-values are the result of the chi-squared test or fisher exact test as appropriate per outcome stratified for OLR versus LLR. Patients who had missing values for the outcome were excluded from the analysis

to malignant liver resection indicates safety of BLT resection in all hospital qualifying for malignant liver resection by sufficient case load.

LLR was associated with reduced postoperative morbidity compared to OLR and similar to outcomes of LLR for liver malignancies in general.[35–37] The current results are similar to previous reports on minimally invasive liver surgery. A nationwide study from the Netherlands showed similar results as the current study (30% vs. 42% of complications after LLR and OLR respectively, p = 0.040).[38] Previous results with regard to laparoscopic BLT resection showed postoperative morbidity incidence of 13.9%; similar to 13% overall 30-day morbidity.[39] This study confirms that if technically feasible, LLR is preferred over OLR concerning resection of BLT.

Potential limitations of this study are registry data associated problems regarding accuracy and coverage. Although third-party data verification deemed 97% of the data accurate, not all specific information concerning operative outcomes could be obtained.[22] Another potential limitation is the lack of information regarding preoperative decision-making process, specific tumour location and preoperative indication for surgery. These were not registered in the DHBA This could have influenced the decision to perform resection of BLT and could be a possible explanation for the surgical intervention in the haemangioma and FNH patients as the European Guideline advocates a wait-and-see policy.[2] Lack of information regarding the preoperative specific tumour location and indication for surgery could thereby lead to confounding by indication despite correction for patient and tumour characteristics. Also, specific tumour location could have been a reason to perform LLR or OLR and this may reflect in the differences in postoperative outcomes. However, this information is not registered in the DHBA and could not be obtained. Another limitation is the lacking of perioperative details such as perioperative outcomes which can be attributed to the audit nature of this cohort.

Future studies will have to be conducted on improving outcomes after BLT resection. Resection of BLT is often performed in young and healthy patients and therefore major complications of any sort should be avoided. BLT resection should be used only in a highly selected group of patients after a weighted shared-decision making process by patient and surgeon. Outcomes such as morbidity and mortality are very important in this process. However, possible influence of BLT resection on quality of life should be part of the evaluation of these patients to further assess which patients benefit from BLT resection.[16,40] The role of a composite outcome measure such as Textbook Outcome, which has been described in other fields, is therefore even more relevant for BLT patients.[41] The authors propose surgeons and treating physicians to aspire results comparable to i.e. donors participating in living liver transplantation.[42] The authors will therefore initiate drafting of an international Textbook Outcome in BLT patients.

In conclusion, 30-day postoperative outcomes after resection of BLT in this nationwide population-based study are good. BLT resection is safe and can be performed when indicated. LLR is preferred over OLR in appropriately selected patients because of short-term benefits. Although the current study encompasses observations in the Netherlands, the nationwide design and inclusion size provides insights for shared decision making as well as an international benchmark for quality evaluation.

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Conflict of interest

None declare.

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Appendix A. Supplementary data

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