



Analysis of open and laparoscopic liver resections in a German high-volume liver tumor center

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Background: Minimally invasive treatment modalities of liver tumors remain a matter of development. This study aims to compare the surgical results and postoperative outcomes of consecutive laparoscopic liver resections (LLR) and open liver resections (OLR) in a German Liver Tumor Center.

Methods: A retrospective data analysis of consecutive patients undergoing LLR and OLR was performed.

Results: A total of n=217 patients were included in the study. Mean patient age was 62±13 years. Forty-three percent (n=93) were treated by minimally invasive surgery. Seventy-seven percent (n=166) of patients were operated for malignant disease and 28% (n=61) had at least one previous upper abdominal surgical intervention. Within the LLR group 61% (n=57) patients received an oncologic tumor resection. With 32% (n=30) hepatocellular carcinoma (HCC) represented the main indication for oncologic LLR, followed by Colorectal Carcinoma Liver Metastases (CRLM) with 13% (n=12) and Cholangiocarcinoma (CCA) with 4% (n=4). Major morbidity (> Clavien Dindo 3b) was 11% (n=23). Morbidity was especially low in the LLR group 5% (n=5) when compared to the OLR 15% (n=18) group. Likewise, overall mortality 6% (n=13) was very low in the LLR group 1% (n=1) when compared to OLR: 10% (n=12) group. In line, mean overall hospital stay was short (14±13 days). With regard to surgical technique, R0 resection in LLR was achieved in 97% (n=90) when compared to OLR 86% (n=107). Overall R0 resection rate was 91% (n=197).

Conclusions: The incidence of complex LLR in our cohort is high. LLR is the preferred surgical strategy for HCC treatment. Satisfactory R0 resection rates, morbidity and mortality rates can be achieved in a high-volume liver tumor center, especially with the application of recently introduced minimally invasive treatment modalities.

Keywords: Open liver resection (OLR); laparoscopic liver resection (LLR); hepatocellular carcinoma (HCC); Colorectal Carcinoma Liver Metastases (CRLM)

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Introduction

Minimally invasive liver surgery is a maturing field (1). Since the initial report in 1992 by Gagner *et al.* (2) the

incidence of laparoscopic liver resections (LLR) has increased exponentially (3). Initial concerns with regard to oncological inferiority and technical inapplicability have

been scientifically disproved and even outplayed by reduced morbidity, and mortality in selected groups of patients (4).

“First movers” in this novel field of minimally invasive liver surgery comprised groups in Asia, the United States and Europe. Consensus guidelines have been established (5) and constantly updated (6) and adapted to anticipated new challenges (7). Today, difficulty scoring methodologies help to estimate and rank the complexity of a minimally invasive liver resection (8). However, open and minimally invasive resections cannot be compared one to one. In contrast to open procedures, which are graded in major and minor, depending on the amount of liver segments resected (according to the Brisbane 2000 terminology) (9), minimally invasive resections of posterosuperior segments, which are difficult to access with conventional laparoscopic instruments, justify for a “technical major” designation (10), which would be classified as minor according to the conventional open surgical terminology.

In recent years there has been a significant increase in the number of series published on LLR, that include single center series. In Germany, our team was among the first to adapt to laparoscopic liver surgery. Initially we shared the opinion that LLR was ideally suited for the resection of Hepatocellular carcinoma (HCC) in patients with cirrhosis (11,12). With an increase in experience and the implementation of open surgical strategies into the minimally invasive liver surgical world, more complex procedures were accomplished to the patients benefits owing to our increasing capability (13). Among other things, this included the implementation of novel intraoperative visualization techniques like hyperspectral imaging (14) and indocyanine green (ICG) staining (15,16). Today laparoscopic hemi-hepatectomies are performed on a regular basis for both malignant and benign indications and even extended resections for perihilar cholangiocarcinoma (pCCA) requiring biliary reconstruction are commonly addressed laparoscopically in specialized liver tumor centers (17). In this study, we aimed to analyze perioperative and short-term postoperative outcomes of our patients requiring liver resection for benign and malignant disease. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/ls-20-93>).

Methods

Our prospectively maintained Liver Tumor Center database for patients undergoing liver resection was analyzed for the years 2018 and 2019. This study was conducted in

congruence with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the University Clinic of Leipzig (Ref. #: 142/18-ek). Because of the retrospective nature of the research, the requirement for informed consent was waived. The primary outcome measure was short-term surgical outcome. All liver resections were performed or assisted by the same two surgeons.

Before surgery, each case was reviewed in a multidisciplinary tumor-board meeting. In principle every patient was primarily evaluated for LLR. This included patients with resectable liver disease, independent of the liver segment affected, and sufficient functional parenchyma and liver function, which was measured by CT volumetry and the LiMAx test (18). Patients with tumor disease of the liver hilus, involving central vascular structures requiring vascular reconstruction during resection, and patients receiving portal vein embolization for liver augmentation, were not considered for LLR at that time.

Patient demographics, pathologic diagnosis, radiologic findings, and peri- and intraoperative surgical data were reviewed. The extent of OLR was graded according to the Brisbane 2000 terminology of liver anatomy and resections (9). LLRs were classified according to both the Asian (8,19) and European (10) difficulty scoring systems. The Clavien-Dindo classification was used for morbidity assessment, and major morbidity was defined as being Clavien Dindo 3b or greater (20).

Surgical technique

Open liver resections (OLR) were performed as described earlier by our group (14,21,22). For laparoscopic resections we preferred a supine patient position with split legs, with the surgeon standing between the legs and the assistant on the left side of the patient. Intraoperative ICG counter perfusion staining was utilized in anatomic liver resections following inflow control and direct ICG tumor staining was employed for intraoperative tumor demarcation of HCC, CCA and CRLM (15). If appropriate, a laparoscopic liver hanging maneuver was utilized for extensive resections to reduce bleeding during the parenchymal phase and furthermore simplify the procedure (13). A tourniquet around the hepatoduodenal ligament was always placed prior to resection, to facilitate a Pringle Maneuver in case of bleeding.

Special laparoscopic instruments comprised ultrasonic shears (Harmonic, Ethicon®) a laparoscopic CUSA (Caviton Ultrasonic Surgical Aspirator), and bipolar forceps.

Table 1 Demographic data and pathologic diagnosis

Variables	LLR (n=98, 42%)	OLR (n=133, 58%)	Total (n=231)	P values
Demographics				
Mean age at operation in years (SD)	59 (14.3)	65 (11.8)	62 [13]	0.002
	Range 24–68	Range 22–85		
Sex-ratio, female/male (%)	45/53 (45.9/54.1)	53/80 (39.9/60.1)		
Pathologic diagnosis				
Malignant	61 (62.2)	118 (88.7)	179 (77.5)	
Colorectal carcinoma liver metastases, n (%)	13 (13.3)	43 (32.3)	56 (24.2)	
Recurrent, n (%)	0	7 (16.3)	7 (12.5)	
Hepatocellular carcinoma, n (%)	31 (31.6)	18 (13.5)	49 (21.2)	
Recurrent, n (%)	2 (6.5)	7 (38.9)	9 (18.4)	
Cholangiocarcinoma, n (%)	5 (5.1)	46 (34.6)	51 (22.0)	
Intrahepatic cholangiocarcinoma, n (%)	4 (80.0)	19 (41.3)	23 (45.1)	
Intrahepatic cholangiocarcinoma recurrent, n (%)	0	4 (8.7)	4 (7.8)	
Perihiliary cholangiocarcinoma, n (%)	1 (20.0)	19 (41.3)	20 (39.2)	
Extrahepatic cholangiocarcinoma, n (%)	0	1 (2.2)	1 (2.0)	
Gallbladder carcinoma, n (%)	0	3 (6.5)	3 (5.9)	
Benign	37 (37.8)	15 (11.3)	52 (22.5)	
Hemangioma, n (%)	8 (8.2)	3 (2.3)	11 (4.8)	
Focal nodular hyperplasia, n (%)	9 (9.2)	0	9 (3.9)	
Liver adenoma, n (%)	7 (7.1)	1 (0.8)	8 (3.5)	
Previous surgeries, n (%)	31 (31.6)	72 (54.1)	103 (44.6)	

Laparoscopic ultrasound was performed for intraoperative tumor visualization and vascular anatomy mapping in every case. All patients undergoing OLR and LLR received overnight intensive care and were discharged to normal care earliest on postoperative day one.

Statistical analysis

Data was collected retrospectively and a database of previously determined variables was generated. A *t*-test was used to determine statistical significance. A *P* value <0.05 was considered as statistically relevant. Statistical analyses were performed using Microsoft excel 2018.

Results

In the time period investigated, a total number of n=231

patients received a liver resection in our institution. An early termination of the operation without resection was necessary in n=14 (7%) of cases due to histologically confirmed peritoneal metastasis which was not detected in the staging CT or MRI and therefore subsequently excluded from the final study population (n=217). Patient demographics and most frequent pathologic diagnoses are displayed in *Table 1*.

In short, n=124 (57%) patients received OLR and n=93 (43%) was operated with a minimally invasive approach (LLR). From all minimally invasive treated patients, n=73 (79%) received a totally laparoscopic operation and n=15 (16%) patients were operated in a laparoscopic-hand-assisted manner. This exclusively applied to resections of the posterosuperior segments 7, 8 and 4a. In n=5 cases (5%) a conversion to open surgery was necessary due to laparoscopic hand-assisted inaccessibility n=4 (80%), or

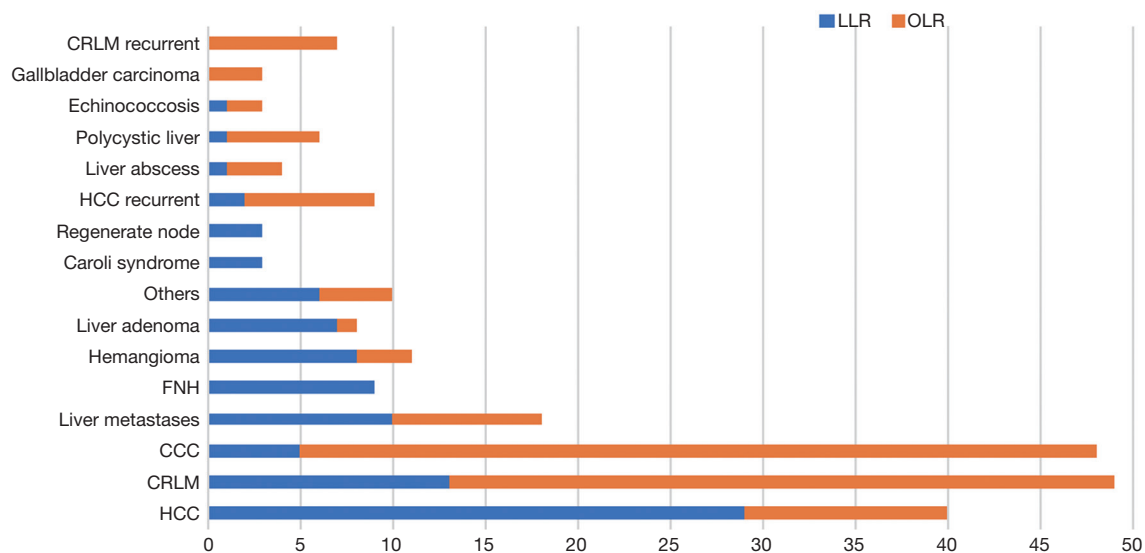


Figure 1 Distribution of LLR and OLR with regard to diagnosis: LLR for HCC n=28 (30.1%), CRLM n=12 (12.9%), Liver metastases n=9 (9.7%), FNH n=9 (9.7%), Hemangioma n=8 (8.6%), Liver adenoma n=7 (7.5%), Others n=6 (6.5%), CCA n= 4 (4.3%), Caroli-syndrome n=3 (3.2%), Regenerate node n=2 (2.2%), HCC recurrent n=2 (2.2%), Liver abscess n=1 (1.1%), Polycystic liver n=1 (1.1%), Echinococcosis n=1 (1.1%). OLR for CCA n=36 (29%), CRLM n=35 (28.2%), HCC n=11 (8.9%), Liver metastases n=8 (6.5%), HCC recurrent n=7 (5.6%), CRLM recurrent n=7 (5.6%), Polycystic liver n=5 (4%), Hemangioma n=3 (2.4%), Others n=4 (3.2%), Gallbladder carcinoma n=2 (1.6%), Liver abscess n=3 (2.4%), Echinococcosis n=2 (1.6%), Liver adenoma n=1 (0.8%).

tumor infiltration into other organs (diaphragm, inferior vena cava) in combination with morbid obesity [n=1, (20%)].

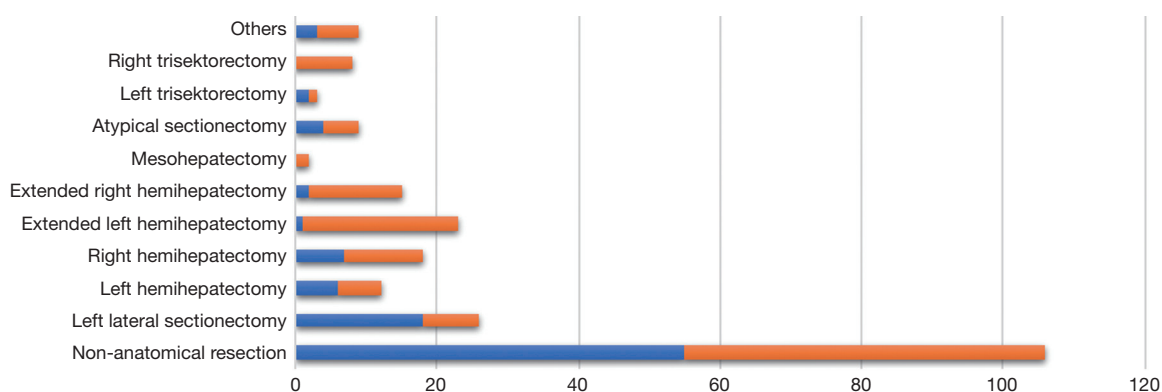
Mean patient age was significantly higher in the OLR group (65±12 years), when compared to the LLR group (LLR: 59±14 years; P=0.002), and the sex ratio (female/male) was in favor of men, in both groups [OLR: f:m=54% (n=51):59% (n=73) *vs.* LLR: f:m=41% (n=43):46% (n=50)], respectively.

A total number of n=166 patients (77%) were operated for malignant disease and n=51 patients (24%) were operated for benign indications. This larger number of oncologic operations remained valid for both open [OLR for malignant indication: n=109 (88%) *vs.* OLR for benign indications: n=15 (12%)] and laparoscopic resections [LLR for malignant indication: n=57 (61%) *vs.* LLR for benign indications: n=36 (39%)].

Patients with Cholangiocarcinoma (CCA) and Colorectal Liver Metastases (CRLM) were predominantly treated by OLR [OLR for CCA: n=42 (34%) *vs.* LLR for CCA: n=4 (4%) and OLR for CRLM: n=42 (34%) *vs.* LLR for CRLM: n=12 (13%)], whereas patients with HCC to a greater extent received a LLR [LLR for HCC: n=30 (32%) *vs.* OLR for HCC: n=18 (15%)]. The three major benign indications for liver resection comprised: giant hemangioma [n=11 (5%)],

symptomatic focal nodular hyperplasia (FNH) [n=9 (4%)] and liver adenoma [n=8 (4%)]. A total number of n=61 (28%) of patients had previous upper abdominal surgery [OLR with prior abdominal surgery n=45 (36%) and LLR with prior abdominal surgery n=16 (19%)]. This included previous liver resections [n=31 (14%)], cholecystectomies [n=20 (9%)], gastric resections [n=7 (3%)], splenectomies [n=2 (1%)] and prior liver transplantation [n=1 (1%)] etc. A detailed distribution of OLR and LLR with regard to the underlying diagnosis is displayed in *Figure 1*.

With regard to the extent of liver surgery, non-anatomical resections [n=101 (47%)] were the most frequent operations in our cohort with n=51 (55%) performed by LLR, and n=50 (40%) performed by OLR. With a total of n=28 (13%) anatomic right and left hemihepatectomies were the second most common surgical procedures, both commonly performed by LLR [left hemihepatectomy LLR: n=6 (7%), *vs.* left hemihepatectomy OLR: n=6 (5%) and right hemihepatectomy LLR: n=7 (8%), *vs.* right hemihepatectomy OLR: n=9 (7%)]. Left lateral (Segment 1 and 2) resections n=26 (12%), were the third most common resections in our cohort, predominantly performed by LLR [left lateral LLR: n=18 (19%) *vs.* left lateral OLR: n=8 (7%)]. In n=33 (15%) cases an extended resection was necessary,



	Non-anatomical resections	Left lateral sectionectomy	Left hemihepatectomy	Right hemihepatectomy	Extended left hemihepatectomy
■ LRR	55	18	6	7	1
■ OLR	51	18	6	11	22

	Extended right hemihepatectomy	Mesohepatectomy	Atypical sectionectomy	Left trisektorectomy	Right trisektorectomy	Others
■ LRR	2	0	4	2	0	3
■ OLR	13	2	5	1	8	6

Figure 2 Type of liver resections: LLR: non-anatomical resections n=51 (54.8%), left lateral sectionectomy n=18 (19.4%), left hemihepatectomy n=6 (6.5%), right hemihepatectomy n=7 (7.5%), extended left hemihepatectomy n=1 (1.1%), extended right hemihepatectomy n=2 (2.2%), atypical sectionectomy n=4 (4.3%), left trisektorectomy n=2 (2.2%), Others n=3 (3.2%). OLR: non-anatomical resections n=50 (40.3%), left lateral sectionectomy n=8 (6.5%), left hemihepatectomy n=6 (4.8%), right hemihepatectomy n=9 (7.3%), extended left hemihepatectomy n=18 (14.5%), extended right hemihepatectomy n=12 (9.7%), Mesohepatectomy n=2 (1.6%), atypical sectionectomy n=4 (3.2%), left trisektorectomy n=1 (0.8%), right trisektorectomy n=8 (6.5%), others n=6 (4.8%).

which was predominantly performed by OLR [LLR: n=3 (3%), OLR: n=30 (24%)]. Two out of 11 trisectionectomies were performed by LLR [Trisectionectomy LLR: 2 (2%) *vs.* Trisectionectomy OLR: 9 (7%)]. Two mesohepatectomies (2%) were performed by open surgery. Laparoscopic lymphadenectomy was performed in patients with CCC and one patient with HCC. A detailed description of types of liver resections performed is given in *Figure 2*.

Surgical data

The mean operative time was longer for OLR with 341 min (range, 141–556 min) when compared to LLR [273 min (range, 44–590 min), ($P < 0.001$)] and intraoperative blood transfusions were necessary in n=7 (3%) cases [intraoperative transfusion LLR: n=3 (3%) *vs.* intraoperative transfusion OLR: n=4 (3%)]. Mean length of hospital stay was 14 ± 13 days (LLR: 9 ± 6 *vs.* OLR: 18 ± 15 days; $P < 0.001$). Abdominal drains were placed in 41% (n=88) of cases [abdominal drain LLR: n=21 (22%) *vs.* abdominal drain

OLR n=67 (54%)]. Intraoperative biliary drainages [n=102 (47%)] were predominantly placed in OLR cases [n=95 (77%)] when compared to LLR cases [n=7 (8%)]. Radical Lymphadenectomy was performed in n=74 cases (34%); [radical lymphadenectomy LLR: n=6 (7%) *vs.* radical lymphadenectomy OLR: n=68 (55%)]. R0 resection was achieved in n=197 (91%) of cases [R0 resection LLR: n=90 (98%) *vs.* R0 resection OLR: n=107 (86%)]. R0 resection rates were highest for CRLM resections [LLR: n=12 (100%) *vs.* OLR: n=38 (91%)] followed by HCC resections [LLR: n=27 (90%) *vs.* OLR: n=16 (89%)] and CCA resections [LLR: n=3 (75%) *vs.* OLR: n=31 (74%)]. A detailed description of surgical results is provided in *Table 2*.

Difficulty scoring and morbidity and mortality outcome

A detailed description of classifications and difficulty scoring of liver resections and complications after liver resection for our patient group is given in *Table 3*. In short, according to the Brisbane 2000 terminology of liver anatomy and

Table 2 Surgical data and results

Variables	LLR (n=98)	OLR (n=133)	Total (n=231)	P values
Mean length of hospital stays in days (SD)	8.3 (7.1)	17.4 (15.0)	13.4 (12.9)	<0.0001
Mean operative time in minutes (range)	266 [44–590]	329 [141–556]	302	<0.0001
Received blood transfusion, n (%)	3 (3.1)	4 (3.0)	7 (3.0)	
Drainage				
Intraabdominal drainage, n (%)	22 (22.4)	72 (54.1)	94 (40.7)	
T-drainage, n (%)	7 (7.1)	95 (71.4)	102 (44.2)	
Lymphadenectomy, n (%)	6 (6.1)	72 (54.1)	78 (33.8)	
R0 resections, n (%)	91 (92.9)	107 (80.5)	198 (85.7)	
Colorectal carcinoma liver metastases, n (%)	12 (92.3)	38 (88.4)	50 (89.3)	
Hepatocellular carcinoma, n (%)	27 (87.1)	16 (88.9)	43 (87.8)	
Cholangiocarcinoma, n (%)	4 (80.0)	31 (67.4)	35 (68.6)	

Table 3 Scoring system and postoperative outcome

Variables	LLR (n=98)	OLR (n=133)	Total (n=231)	P values
Scoring system				
Di Fabio <i>et al.</i> major hepatectomy (%)	38 (38.8)			
LTMH (%)	17 (44.7)			
LPMH (%)	21 (55.3)			
Ban <i>et al.</i>			11 (11.2)	
Low [1–3]	1 (n=3), 2 (n=0), 3 (n=8)			
Intermediate [4–6]	4 (n=22), 5 (n=3), 6 (n=18)		43 (43.9)	
High [7–10]	7 (n=21), 8 (n=2), 9 (n=14), 10 (n=7)		44 (44.9)	
Brisbane 2000 major (%)		72 (54.1)		
Minor (%)		61 (45.9)		
Clavien-Dindo no complication	68 (96.4)	47 (35.3)	115 (49.8)	
I	12 (12.2)	20 (15.0)	32 (13.9)	
II	6 (6.1)	20 (15.0)	26 (11.3)	
IIIa	6 (6.1)	15 (11.3)	21 (9.1)	
IIIb	4 (4.1)	13 (9.8)	17 (7.4)	
IVa	1 (1.0)	6 (4.5)	7 (3.0)	
IVb	0	0	0	
V	1 (1.0)	12 (9.0)	13 (5.6)	
Morbidity, n (%)	5 (5.1)	19 (14.3)	24 (10.4)	
Mortality, n (%)	1 (1.0)	12 (9.0)	13 (5.6)	

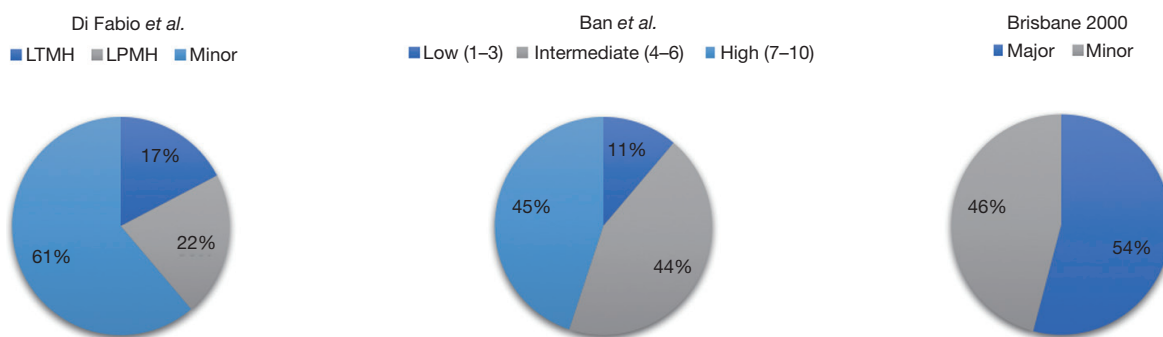


Figure 3 Overview of difficulty scoring and Brisbane 2000 classifications of liver resections: Di Fabio *et al.*: the laparoscopic group got classified based on major hepatectomy in n=16 (17%) LTMH and n=20 (21%) LPMH. Ban *et al.*: the laparoscopic group got classified according to difficulty in n=7 (8%) low difficulty, n=42 (45%) intermediate and n=44 (47%) high. Brisbane 2000: the open group got divided in n=64 (52%) major and n=60 (48%) minor resections.

resections, n=64 (52%) patients were treated by major and n=60 (48%) by minor resections.

According to Di Fabio *et al.* out of n=93 LLRs, n=36 (39%) was classified as laparoscopic major hepatectomies comprising n=16 (44%) traditional major laparoscopic hepatectomies (LTMH) and n=20 (56%) laparoscopic posterosuperior major hepatectomies (LPMH), which were technically challenging as they are considered difficult to approach using straight laparoscopic instruments.

According to Ban *et al.* out of the n=93 minimally invasive operated LLRs, n=7 (8%) was of low, n=42 (45%) was of intermediate and n=44 (47%) was of high difficulty, with regard to performance (Figure 3).

Major morbidity, defined as Clavien Dindo 3b or greater was 11% (n=23). Patients with LLR had a significantly lower morbidity [morbidity rate LLR: n=5 (5%)] when compared to the OLR group [morbidity rate OLR: n=18 (15%)]. Likewise, overall in-hospital mortality n=13 (6%) was very low in the LLR group [in hospital mortality LLR: n=1 (1%)] when compared to OLR group [in hospital mortality OLR: n=12 (10%)].

Discussion

Our data demonstrate that despite high numbers of complex liver resections, morbidity and mortality rates were low in our analyzed patient group. The fact that a fraction of more than 42% of all liver resections were performed minimally invasive in the years 2018 and 2019, furthermore reflects our key of propelling minimal invasive surgical techniques for the liver.

The majority (77%) of our patients received an

oncologic resection. This was true for both OLR and LLR and resembles the global attitude that minimally invasive techniques are not reserved for selected tumor entities. However, in parallel we would like to strike that the indication for a liver resection must not be loosened especially for benign indications just because of minimal invasive accessibility (23).

Patients with HCC in cirrhosis accounted for the major part of LLRs in our collective. Analysis of the literature confirms that minor liver resections for HCC even in cirrhotic livers should be the approach of first choice (24). This might especially be true for lesions less than 5 cm in diameter (25). A recent propensity score matched analysis demonstrated that in terms of oncologic outcome and surgical outcome, a selected group of patients even might benefit from major LLR for HCC in cirrhosis (26). Decades ago, it has been shown that liver resection prior to transplantation did not increase the morbidity or impair long-term survival following liver transplantation (27). Recent work indicated that salvage liver transplantation after laparoscopic resection for HCC was even more feasible and save, achieving excellent short-term results (28). A recent meta-analysis demonstrated that surgical resection also achieved a better overall-survival when compared to Trans Arterial Chemo Embolization (TACE) in patients with HCC. Therefore laparoscopic resections might be able to partially replace TACE as a bridging therapy to liver transplantation. However, it is clear that efficient bridging strategies for patients with HCC are even more important (29) especially in countries like Germany where waiting time for liver transplantation is long.

Few patients diagnosed with CCA received LLR in

our cohort. In this patient collective a minimally invasive approach was predominantly considered for intrahepatic Cholangiocarcinomas (iCCA), which did not require extrahepatic bile duct resection. A recent meta-analysis confirmed that LLR for iCCA achieved excellent surgical outcomes and provided short-term benefits over OLR without negatively affecting oncologic adequacy in terms of R0 resections and disease recurrence (30). Our patient collective only comprised one case with perihilar Cholangiocarcinoma (pCCA) which required Roux – Y laparoscopic bile-duct reconstruction. Similar cases have been published as case reports recently (31). Surgical resection still represents the mainstay of pCCA treatment (32). However, if laparoscopic surgery is capable to replace our initially postulated open surgical resection strategy for pCCA (21) requires further investigations.

Radical lymphadenectomy is mandatory in patients with CCA. Recent data indicate that the laparoscopic technique does not compromise accuracy and outcome of nodal dissection (33,34). From a technical perspective, delicate vascular reconstruction after portal vein resection and biliary reconstruction, represents the “Achilles heel” of a pCCA resection. Performance of vascular and biliary reconstruction with laparoscopic instruments is even more challenging. To overcome the hurdle of restricted visibility and maneuverability we recently introduced a parachute suturing technique for biliary reconstruction in patients receiving a laparoscopic pCCA resection (35). This technique provided a superior view on the anastomosis and facilitated an unrestrained completion of the anastomosis. Although robotic surgery is supposed to deliver substantial benefits over laparoscopic surgery especially when it comes to delicate vascular reconstruction, first data do not support its continued practice on pCCA cases until significant technical and instrumental refinements become available (36).

The liver is the most common site of metastasis in patients with colorectal cancer. In Europe the overall liver metastasis rate from colorectal cancer has been reported to be up to 23% (37). Surgical resection is currently still the only curative treatment modality. The OSLO-COMET randomized controlled trial demonstrated that in patients undergoing parenchyma-sparing liver resection for colorectal metastases, laparoscopic surgery was associated with significantly less postoperative complications when compared to open surgery (38). Patients with CRLM represent the centerpiece of our study population. However, only a fraction of 13% was treated by LLR. High tumor load requiring future liver remnant

augmentation strategies (39) were the main reason for the necessity of an OLR strategy. Up to 14% of CRLM may be synchronously detected (40). As described by other groups, in case of synchronous liver metastases, we favored a simultaneous laparoscopic resection (together) rolled into one with primary tumor resection. Provided that the extent of liver resection required was minor (41), including wedge resections, single segmentectomies or left lateral resections. In case of higher tumor loads chemotherapy was administered prior to major liver resection (42).

The basis of a curative liver resection is built on negative resection margins. Overall R0 resection rate was 91%. Our data show that LLR achieved better R0 resection rates than OLR, however this was not a case matched study, and a direct comparison is hence invalid. Nevertheless, our data demonstrate that at least the introduction of LLRs into our program did not impair R0 resection rates. The margin status remains a very important factor in hepatectomies independent of the tumor entity.

Benign liver tumors represent a challenge in clinical management and there is considerable controversy with respect to the indications for surgery as the evidence for surgical treatment is variable (43). Recent data indicate that patients with preoperative symptoms from adenoma and focal nodular hyperplasia (FNH) show a high rate of postoperative symptom relieve (44). From a global perspective, most initial minimally invasive liver resections were typically done for benign lesions in anterior or left lateral segments (45). In our patient group the majority of benign lesions was operated by LLR.

Difficulty scoring and correct taxonomy for liver resections is vital for the establishment and maintenance of an academic liver surgery program. It is not only key for the scientific evaluation of patient data and quality assessment but also helps trainees in their buildup of surgical skills. Especially in the field of minimally invasive surgery difficulty scoring is required to guide surgeons in advancing from simple to difficult resections. We applied the two most common difficulty scoring systems used in Asia and Europe to our patient cohort. Ban *et al.* provided a scoring system based on preoperative parameters which comprise the extent of liver resection, tumor location, tumor size, liver function, and tumor proximity to major vessels (8,19). Accordingly, difficulty of laparoscopic resections can be graded as low, intermediate and high. Di Fabio *et al.* highlighted the fact that liver resections of segments from the posterosuperior segments may be graded as technically major if performed laparoscopically due to the difficult laparoscopic

accessibility of these segments. A recent landmark paper by Filmann *et al.* revealed that overall hospital mortality after liver resection is high in Germany (46). With an overall hospital mortality rate of 5.9% for our cohort we were able to achieve good results. Especially the low mortality rate of 1% in the LLR group confirms that our development of a minimally invasive liver resection program should be on the right track.

The learning curve in laparoscopic liver surgery consists of different phases in which hepatobiliary surgeons stepwise edge through more and more complex cases (47). We started our program with smaller resections of left lateral and anteromedial segments predominantly in patients with HCC in liver cirrhosis (12). Little by little we gained more confidence in doing anatomic hemihepatectomies and even extended liver resections (13). We share the opinion that major hepatectomies might have a learning curve of 45–60 cases (48). With a case load of 60–100 LLRs per year we are well aware that it takes time to accomplish individual goals. In our unit all laparoscopic resections were performed by the same surgical team. With an experience of more than 7 years we currently aim to establish a training program for fellows interested in minimally invasive liver surgery. In this context we share the opinion that inter-institutional collaboration and exchange of skills might enable a synergistic development of techniques for safe progression to more complex surgeries (49). The fact that we are still operating on a highly selected patient collective however makes a general comparison to open liver surgery cases difficult.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in congruence with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committee of the University Clinic of Leipzig (Ref. #: 142/18-ek). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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