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Multivariate analysis of risk factors for postoperative complications after laparoscopic liver resection

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Abstract
Background The identification of modifiable perioperative risk factors in patients undergoing laparoscopic liver resection (LLR) should aid the selection of appropriate surgical procedures and thus improve further the outcomes associated with LLR. The aim of this retrospective study was to determine the risk factors for postoperative morbidity associated with laparoscopic liver surgery.
Methods All patients who underwent elective LLR between January 1999 and December 2012 were included. Demographic data, preoperative risk factors, operative variables, histological analysis, and postoperative course were recorded. Multivariate analysis was carried out using an unconditional logistic regression model.
Results Between January 1999 and December 2012, 140 patients underwent LLR. There were 56 male patients (40 %) and mean age was 57.8 ± 17 years. Postoperative complications were recorded in 30 patients (21.4 %). Postoperative morbidity was significantly higher after LLR of malignant tumors [$n = 26$ (41.3 %)] when compared to LLR of benign lesions [$n = 4$ (5.2 %) ($P < 0.0001$)]. By multivariate analysis, operative time [OR = 1.008 (1.003–1.01), $P = 0.001$] and LLR performed for malignancy [OR = 9.8 (2.5–37.6); $P = 0.01$] were independent predictors of postoperative morbidity. In the subgroup of patients that underwent LLR for malignancy using the same multivariate model, operative time was the sole independent predictor of postoperative morbidity [OR = 1.008 (1.002–1.013); $P = 0.004$].
Conclusions Postoperative complication rate increases by 60 % with each additional operative hour during LLR. Therefore, expected operative time should be assessed before and during LLR, especially when dealing with malignant tumor.

Keywords Hepatectomy · Laparoscopy · Liver · Morbidity

Laparoscopic liver resections (LLR) were originally confined to small wedge resections [1]. However, technical refinement of procedures and progress in anesthesia have enabled more extensive resections, such as right hepatectomies [2–4], left hepatectomies [5], and even extended right and left hepatectomies [6, 7].

Several comparative studies have suggested that laparoscopy is associated with less bleeding [8–11], fewer postoperative complications [8, 9, 11–14], less frequent administration of analgesics [15, 16], shorter length of hospital stay [10–12], and a higher cost effectiveness [17] than open surgical procedures. Several authors consider laparoscopy as the gold standard for several procedures, such as left lateral sectionectomy [18, 19]. Growing interest of the surgical community in LLR led to the first international consensus meeting on laparoscopic liver surgery, which was held in November 2008 at Louisville

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(USA) [20]. Members of this meeting concluded that the acceptable indications for LLR are solitary liver nodules 5 cm or less in size located in liver segments II, III, IVb, V, or VI.

Nevertheless, concerns persist regarding difficulties in liver mobilization and transection, risks of major intraoperative bleeding, gas embolism, and dissemination of malignant tumors. These concerns were responsible for the initial slow introduction of LLR, and currently most LLR are still performed in expert centers [21]. Intraoperative adverse events may negatively affect immediate or late patient outcomes and the acceptance of the use of LLR in general practice depends on our ability to minimize their occurrence. The identification of modifiable perioperative risk factors in patients undergoing LLR should aid the selection of appropriate surgical procedures and thus improve further the outcomes associated with LLR.

The first LLR was undertaken at the Antoine Béclère Hospital in Clamart in 1998. The aim of this study was to determine the risk factors for postoperative morbidity associated with laparoscopic liver surgery. This was a prospective study carried out with a database detailing LLR that was performed at our center.

Methods

All patients who underwent elective LLR between January 1999 and December 2012 were included. Data were prospectively recorded and retrospectively analyzed.

Patient selection

Each patient was preoperatively evaluated by computed tomographic (CT) scan with contrast injection. Patients were considered operable if all tumors could be treated by radical resection with macroscopically negative surgical margins and a sufficient future liver remnant volume. In patients with a future liver remnant volume considered to be insufficient (<30 % of the total liver volume or <40 % for pathologic underlying liver), preoperative portal vein embolization was carried out. As defined by the 2008 international consensus of Louisville [22], patients with solitary lesions of 5 cm or less, located in liver segments II to VI, at distance from the line of transection, the hepatic hilum, and the vena cava were considered as more suitable to LLR (Louisville criteria). However, those criteria were not exclusive and each patient's medical file was discussed in a multidisciplinary meeting.

In our center, exclusion criteria were tumors well close from the portal pedicle or hepatic veins, an American Society of Anesthesiologists score (ASA) exceeding 3, a decompensated cirrhosis (Child B or C), esophageal varices grade >1 and a platelet count $<80 \times 10^9$/l. We do not consider patient weight a contraindication as previous upper abdominal surgery.

Operative and perioperative management

Our surgical technique of LLR has been previously described [2, 8, 23, 24]. Briefly, we used an entirely laparoscopic technique with five ports, a 10–12 mmHg pneumoperitoneum and a 0° or 30° laparoscope. Parenchymal transection was performed by ultrasound dissection (Ultracision; Ethicon, Issy les Moulineaux, France) or thermofusion (Ligasure; Covidien, Elancourt, France). Bipolar coagulation was used to treat minor bleeding. The resected liver was placed in a plastic bag and extracted, without fragmentation, through a suprapubic horizontal incision. Pringle's maneuver was not used. In accordance with the results of literature [25], abdominal drains were not positioned at the time of LLR. The hand-assisted technique was not used. In anatomic resections, portal vessels and hepatic veins were controlled outside the liver and divided before parenchymal transection [23].

Single incision laparoscopic procedures were performed through a 2-cm incision on the umbilicus with an approved disposable 4 instruments channels trocar (Quadriport, Olympus, France). A flexible laparoscope system (endoEYE, Olympus, France) was used with a nondisposable double curved grasper to avoid instruments crossing.

All patients received antibiotic prophylaxis. A daily subcutaneous injection of low-molecular-weight heparin sodium was started as a prophylactic against deep venous thrombosis on postoperative day (POD) 0 or when prothrombin time (PT) reached more than 50 %, according to the surgeon's decision. This treatment was maintained during the hospitalization or during 6 weeks in case of malignant tumor. Patients were seen daily until hospital discharge.

Demographic data, preoperative risk factors, operative variables, histological analysis, and postoperative course were recorded. Parameters on postoperative liver failure [26] (i.e., PT, liver transaminases, γ-glutamyl transpeptidase, alkaline phosphatase, and bilirubin) were measured on POD 1, 3, and 5 in case of major resection and/or pathologic underlying liver. Pathologic underlying liver was defined as liver cirrhosis, fibrosis (metavir F1-F3), and steatosis (≥10 %). In suspected cases of thoracic or abdominal complication, a thoracoabdominopelvic CT scan was performed. Major hepatectomy was defined as the resection of 3 or more segments. Mortality and morbidity were defined as death or complications occurring within 30 days after surgery. Complication severity was stratified according to the modified Clavien classification [27].

Statistical analysis

Statistical analysis was carried out with SPSS software (IBM Company, Los Angeles, CA). Continuous variables were expressed as mean ± SD and were compared using the student *t* test or the Mann–Whitney *U* tests, as appropriate. χ^2 test or Fisher's exact test were used for comparisons of categorical variables, as appropriate. Values of $P < 0.05$ were considered statistically significant. Multivariate analysis was carried out using a logistic regression model expressed as an odds ratio (OR). To test the independence of the risks factors, the significant pre and intraoperative variables in the univariate analysis were entered into a multivariate logistic regression model with likelihood ratio forward selection.

Results

Patients

Between January 1999 and December 2012, 140 patients underwent LLR. There were 56 male patients (40 %) and mean age was 57.8 ± 17 years. Thirty-four patients (24.3 %) were older than 70 years and 23 (16.4 %) were classified as ASA 3. The mean body mass index (BMI) was 25.5 ± 4.6 kg/m^2 and 13 patients (9.3 %) were obese (BMI > 30 kg/m^2). Sixty-one patients (43.5 %) had previous abdominal surgery including 11 patients (7.8 %) who had previous liver resection.

Major hepatectomy was performed in 20 patients (14.2 %). Five procedures (3.6 %) were performed by single incision approach, and 9 patients (6.4 %) required an additional extrahepatic procedure [colectomy ($n = 4$), common bile duct resection ($n = 2$), small bowel resection ($n = 1$), ovariectomy ($n = 1$), gastrectomy ($n = 1$)].

Mean tumor size was 48.9 ± 32.9 mm and 51 tumors (36.4 %) were ≥5 cm. Multiple tumors were resected in 8 patients (5.7 %). Tumors were located in the anterior segments (II, III, IVb, V, and VI) in 73 patients (52.1 %). Sixty-three patients (45 %) underwent resection of malignant tumors. The underlying liver was pathologic (fibrotic, cirrhotic, or fatty) in 63 patients (45 %).

Intra- and postoperative course

Mean operative time was 209 ± 119 min. Mean blood loss was 323 ± 443 ml and 42 patients (30 %) had blood loss ≥300 ml. Twelve patients (8.6 %) were transfused during the procedure. Conversion to open procedure was necessary in 7 patients (5 %) due to a bleeding which was temporarily controlled before conversion, and there was no need for emergency laparotomy in life-threatening conditions.

Mean length of stay was 6.7 ± 8.3 days. Postoperative complications were recorded in 30 patients (21.4 %) and included vomiting ($n = 3$), symptomatic pleural effusion ($n = 1$), urinary tract infection ($n = 3$), bleeding from trocar incision ($n = 1$), pulmonary embolism ($n = 1$), pneumonia ($n = 1$), hemorrhage ($n = 3$), ascites ($n = 2$), biliary leakage ($n = 5$), incisional abscess ($n = 2$), liver failure ($n = 3$), cardiac dysrhythmia ($n = 1$), multi-organ dysfunction ($n = 3$), and renal failure ($n = 1$). Distribution of the highest grade complication in each patient after LLR according to the severity index is reported in Table 1. Eventually 5 patients (3.5 %) expired in the postoperative period as a result of liver failure multi-organ failure ($n = 3$), liver failure ($n = 1$), and renal failure ($n = 1$). Of the 5 patients who died in the postoperative period, 4 patients underwent surgery for an HCC, including 3 cirrhotic patients. Two of them required a conversion for a bleeding. The last patient was a 78-year-old woman who underwent a laparoscopic right hepatectomy for a large symptomatic benign lesion (angioma) and expired 11 days after surgery of multi-organ failure (after a mesenteric ischemia). The mean operative time was significantly superior in the group of patients that died in the postoperative period compared with the mean operative time of other patients [390 ± 179 vs. 202 ± 112 min ($P = 0.0005$), respectively].

According to Louisville criteria [22], 72 patients (51.4 %) presented a tumor considered as a favorable indication for LLR, whereas the tumor was outside the criteria in 68 patients (48.6 %). There was no significant difference in morbidity of patients with tumors inside and outside the Louisville criteria (23.5 % vs. 19.4 %; $P = 0.67$). Postoperative morbidity was significantly higher after LLR of malignant tumors [$n = 26$ (41.3 %)] when compared to LLR of benign lesions [$n = 4$ (5.2 %) ($P < 0.0001$)].

Eleven factors were found to be risk factors for postoperative complications: male sex ($P = 0.003$), advanced age (>70-year old) ($P < 0.0001$), obesity ($P < 0.0001$), ASA score = 3 ($P < 0.0001$), major hepatectomy ($P < 0.0001$), malignancy ($P < 0.0001$), operative time ($P < 0.0001$), blood loss ≥300 ml ($P < 0.0001$), transfusion ($P < 0.0001$), length of stay ($P < 0.0001$), and conversion ($P < 0.0001$). Univariate analysis is summarized in Table 2.

By multivariate analysis, operative time [OR = 1.008 (1.003–1.01); $P = 0.001$] and LLR performed for malignancy [OR = 9.8 (2.5–37.6); $P = 0.01$] were independent predictors of postoperative morbidity. Receiver-operating characteristic (ROC) curve revealing the impact of the operative duration on postoperative complication risk is reported in Fig. 1.

Table 1 Distribution of morbidity after laparoscopic liver resection according to the severity index

Dindo I	Vomiting	3 (10 %)
	Pleural effusion	1 (3.3 %)
Dindo II	Urinary tract infection	3 (10 %)
	Bleeding from trocar incision	1 (3.3 %)
	Pulmonary embolism	1 (3.3 %)
	Pneumonia	1 (3.3 %)
	Hemorrhage	2 (6.6 %)
Dindo IIIa	Ascites	2 (6.6 %)
	Biliary leakage	2 (6.6 %)
Dindo IIIb	Biliary leakage	3 (10 %)
	Incisional abscess	2 (6.6 %)
	Hemorrhage	1 (3.3 %)
Dindo IVa	Liver failure	2 (6.6 %)
	Cardiac dysrhythmia	1 (3.3 %)
Dindo IVb	–	0
Dindo V	Liver failure	1 (3.3 %)
	Multi-organ dysfunction	3 (10 %)
	Renal failure	1 (3.3 %)

In the subgroup of patients that underwent LLR for malignancy using the same multivariate logistic regression model, operative time was the sole independent predictor of postoperative morbidity [OR = 1.008 (1.002–1.013); $P = 0.004$].

Discussion

The careful selection of patients for laparoscopic hepatic resection is a prerequisite for a favorable course of surgery (both intraoperative and postoperative) and for a good long-term outcome. Patient selection criteria for LLR have been established by an international consensus on laparoscopic liver surgery [22]; therefore, no study has specifically focused on risk factors for postoperative complications. We used multivariate analysis and found that malignancy and prolonged operative time were independent predictors of postoperative morbidity.

Oncologic outcomes after laparoscopic resection of colorectal liver metastases [28, 29] and hepatocellular carcinoma [8] have been reported in several series of patients. This shows that LLR achieves equivalent resection margins, similar long-term survival, and similar hepatic recurrence rates as open liver resection. Emerging data even suggests that oncologic outcomes associated with minimally invasive surgery are more favorable than those associated with conventional open surgery. Laurent et al. [13] reported that patients with HCC had a better 3-year overall survival after LLR than after open surgery. Indeed, studies have shown that open surgery results in high systemic levels of proinflammatory biomarkers (circulatory cytokines and vascular endothelial growth factor) that are implicated in tumor growth, survival, and proliferation [30]. In addition, enhanced recovery and reduced postoperative complications after laparoscopic surgery may facilitate the early use of adjuvant therapy, which may also improve outcomes for cancer patients [31]. Here, we show that malignancy is an independent risk factor for postoperative complication after LLR. Indeed, cancer patients are particularly sensitive to surgical stress because of cancer related immunosuppression, malnutrition, and neoadjuvant treatment. Furthermore, postoperative complications have a direct effect on recurrence rate and survival in patients with cancer [32, 33], and special care must be given to these patients. A substantial assessment of the use of LLR for patients with cancer is necessary to provide cancer patients with knowledge of the advantages of laparoscopy, in addition to the drawbacks related to potential postoperative complications.

The existence of a direct relationship between operative time and risk of postoperative infection was first demonstrated in 1960 [34, 35]. More recently, Manilich et al. identified operative time as an important risk factor for postoperative complications in a large series of patients undergoing colorectal surgery [36]. Likewise, operative time was identified by multivariate analysis as an independent risk factor for pulmonary and infectious complications after open hepatic resection [37]. The odds ratio in our patient series is low, and shows that the risk of postoperative morbidity is multiplied by 1.008 with each additional operative minute. This risk increases up to 1.61 with each additional operative hour. Vigano et al. evaluated the ‘learning curve’ of LLR [38]. They divided LLR according to the year they were carried out (approximately 60 procedures per three year period) and found that operative duration and postoperative morbidity substantially decreased as time progressed. Thus, especially during the initial learning period, laparoscopic liver procedures that are expected to take a long time should be considered for primary open resection or early conversion.

An international consensus concluded that the most favorable indications for the LLR are a solitary lesion of 5 cm or less [22]. In our department, a tumor size larger than 5 cm was initially considered as a limiting factor, but with increasing experience we were able to extend our criteria. We currently believe that tumor size alone is not a contraindication for laparoscopy and that the surgical approach depends mostly on tumor location in the liver and its position in relation to large vessels [8]. Neither tumor size nor the number of lesions was correlated with morbidity in multivariate analysis. This analysis also showed

Table 2 Preoperative, intraoperative, and postoperative risk factors for complications according to univariate analysis

	No complications ($n = 110$)	Complications ($n = 30$)	*P*
Patients			
Sex (F/M)	66/34	11/19	0.003
Age (years) ± SD	55.4 ± 14.6	65.8 ± 14.1	0.001
Age >70-year old, *n* (%)	17 (15.4)	17 (56.6)	<0.0001
BMI (kg/m^2) ± SD	24.5 ± 4.1	27.5 ± 6.5	0.08
BMI >30 kg/m^2, *n* (%)	6 (5.4)	7 (23.3)	<0.0001
ASA score = 3, *n* (%)	10 (9)	13 (43.3)	<0.0001
Previous abdominal surgery, *n* (%)	44 (40)	17 (56.6)	0.84
Into Louisville criteria*, *n* (%)	58 (52.7)	14 (46.7)	0.68
Surgery			
Major hepatectomy, *n* (%)	9 (8.1)	11 (36.6)	<0.0001
Single incision LLR, *n* (%)	4 (3.6)	1 (3.3)	0.84
Associated extrahepatic procedure, *n* (%)	6 (5.4)	3 (10)	0.47
Tumor and liver characteristics			
Tumor size (mm) ± SD	48.2 ± 31.2	44.6 ± 30.6	0.58
Tumor size ≥5 cm, *n* (%)	38 (34.5)	13 (43.3)	0.82
Multiple lesions, *n* (%)	5 (4.5)	3 (10)	0.46
Anterior segments** localization, *n* (%)	57 (51.8)	16 (53.3)	1.0
Malignant tumor, *n* (%)	37 (33.6)	26 (86.6)	<0.0001
Pathologic underlying liver***, *n* (%)	47 (42.7)	16 (53.3)	0.12
Intra and postoperative results			
Operative time (min) ± SD	177 ± 93	300 ± 147	<0.0001
Blood loss (ml) ± SD	202 ± 205	718 ± 657	<0.0001
Blood loss (ml) ≥ 300 ml, *n* (%)	22 (20)	20 (66.7)	<0.0001
Transfusion, *n* (%)	2 (1.8)	10 (33.3)	<0.0001
Conversion, *n* (%)	0	7 (23.3)	<0.0001
Length of stay (days) ± SD	4.2 ± 3	14.6 ± 13.7	<0.0001

BMI body mass index, *ASA* American Society of Anesthesiologists physical status score, *LLR* laparoscopic liver resection, *SD* standard deviation

* Louisville criteria: solitary lesions of 5 cm or less, located in liver segments II to VI

** Segments II, III, IVb, V, and VI

*** Fibrotic and cirrhotic liver, fatty liver disease

that the criteria from the Louisville consensus were not associated with morbidity.

Although LLR of lesions situated in the posterosuperior part of the liver is technically challenging, we did not identify tumor location as a risk factor for postoperative morbidity. Patients with large lesions in segments VII and/or VIII are usually considered for a laparoscopic approach if a right hemihepatectomy is required, mainly due to the proximity to the right hepatic vein. If a nonanatomic resection is required then patients are generally considered for laparoscopy if the lesion is small and superficial [39]. Only a few anatomical posterior resections were performed in our patient series, and we decided to use an open approach for most tumors requiring an anatomical resection in the posterior part of the liver. This attitude may have underestimated the effect of tumor location on postoperative morbidity. However, we strongly believe that the surgical approach should not alter the amount of liver removed, and the use of laparoscopy does not mean that an isolated segment VII or VIII resection has to become a right hepatectomy.

Operative duration depends of surgeon's experience, the type of liver resection and patient and tumor's characteristics. Large atypical resections can sometimes last longer then some major anatomical resection. Thus, it is very difficult to define what is the exact time cut-off where the surgeons should think about converting. However, when we look at the ROC analysis, we can see that at approximately 200 min of surgery, we reach the better balance between specificity and sensitivity of predicting a postoperative complication. Therefore, when a procedure last more than 3 h, and the surgeon encounters a persistent

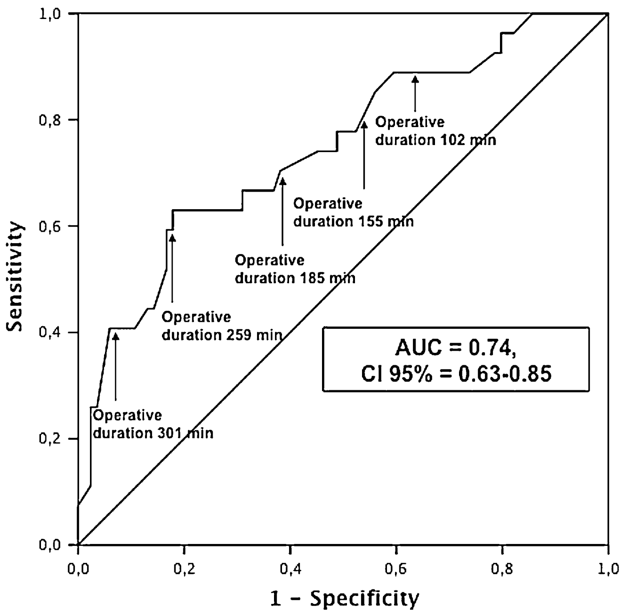

Fig. 1 Receiver-operating characteristic (ROC) *curve* revealing the impact of the operative duration on postoperative complication risk. *CI* confidence interval, *AUC* area under the *curve*

difficulty to progress, it seems rational to consider conversion.

In conclusion, postoperative complication rate increases by 60 % with each additional operative hour during LLR. Therefore, expected operative time should be assessed before and during laparoscopic liver surgery, especially when dealing with malignant tumor.

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