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Research Article

Does Laparoscopic Liver Resection Have Greater Incidence of Bile Leak Compared to the Open Approach?

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1. Abstract

1.1. Background: Biliary leak is the most frequent complication in liver resections. The Second International Consensus Conference mentions a potentially higher incidence of bile leaks in Laparoscopic Liver Resection (LLR) that still needs to be evaluated. The objective of the study is to compare the incidence of bile leaks, using the definition of IGSLL, between open liver resection (OLR) and LLR in a center with the same technique of dividing the parenchyma for both laparoscopic and open surgery.

1.2. Methods: it is a retrospective comparative study that compares two series of liver resections. We included all patients operated between March/2008 and July/2016 by laparoscopic and open approach. Demographic and operative variables, histopathology data and morbidity and mortality were compared.

1.3. Results: A total of 143 liver resections were performed in the study period, but only were included 119 in the analysis: 65 OLR and 54 LLR. The overall morbidity was lower in the laparoscopic group (p=0.011). There were no differences in major complications. From the specific analysis of bile leaks, no overall differences were found (ISGLS A, B, and C) (p = 0.450). There was only one 90-day mortality in the OLR.

1.4. Conclusions: There are no differences in the incidence of bile leaks between LLR and OLR when the same technique of parenchymal transection is used. A possible bias, in addition to sample size and the retrospective study, is case selection: there is a possible bias of indicating open surgery to the most difficult cases.

2. Keywords: Laparoscopic; Liver resection; Bile leak; Open liver resection

3. Background

Hepatic liver resection is one of the procedures that has evolved in the last decades, with a drastic decrease in morbidity and mortality, and is now the treatment of choice for many liver tumors [1]. Bile leak and biliary fistulas are frequent complications in hepatic resections, with an incidence ranging between 4.8% and 7.6% in the large world series [2]. Its consequences are prolongation of the hospital stay, the increase of intra-abdominal septic complications and the secondary liver failure with and mortality. Although bile leak has been precisely defined by the International Study Group for Liver Surgery (ISGLS) Consensus, there are still reports that do not use it or question it, so the actual incidence remains controversial [3].

On the other hand, Laparoscopic Liver Resections (LLR) has been increasing their indications, and precise recommendations have been made for these in the

Second International Consensus held in Marioka-Japan in October 2014. But, when consensus refers to bile leak, it mentions a possible higher incidence of these in LLR that still needs to be evaluated [4].

A recent multicenter study on bile leak in major LLR found no greater incidence compared to large series of open liver resection (OLR) [5]. The only comparative study that specifically focus on bile leak and technique of parenchyma transection (mechanical sutures vs standard crush clamping technique) concludes that the use of mechanical sutures is associated with a greater number of bile leaks [6].

In our center we used, practically in all cases, the crush clamping technique and ultrasonic scalpel for the transection of the liver parenchyma, and used the mechanical suture only for section of large vessels.

Although, because we use the same method of parenchymal transection in both approaches (laparoscopic and open), the question arises whether the LLR, without changing the technique of liver parenchyma transection, is associated with a higher incidence of bile leak.

The objective of the present study is to compare the incidence of bile leak, using the definition of IGSLL, between OLR and LLR in a center with the same technique of dividing the liver parenchyma for both laparoscopic and open surgery.

4. Methods

A retrospective study was carried out on a prospective database comparing two series of consecutively liver resections at the British Hospital of Buenos Aires. We included all patients operated between March 2008 and July 2016 by laparoscopic or open approach.

In order to homogenize the study population, the following exclusions criteria were used:

- Liver resections with a bilioenteric anastomoses, because they can present anastomotic bile leak.

- Isolated caudate resections because we don´t have any cases in the LLR group.

- Non-resective procedures on the liver as the only treatment, such as radiofrequency ablation, alcoholization, liver cysts, etc., and the first stage of a two stages hepatectomy if there was no liver resection.

- Our contraindication criteria to the laparoscopic approach: Right hepatectomies in living donor patients, trisectionectomies, liver resections of lesions located near the confluent of the suprahepatic vein or vena cava.

- Multiple bilateral liver lesions (multiple define as more than 5 lesions).

To assess whether both groups were similar, we compared:

1- Demographic data listed in Table 1.2- Operative variables: type of liver resection according to the Brisbane classification [7], associated procedures on the liver, operative, pedicle clamping and duration, transfusions, and intraoperative events using a new classification [8].

2- Operative variables: type of liver resection according to the Brisbane classification [7], associated procedures on the liver, operative, pedicle clamping and duration, transfusions, and intraoperative events using a new classification [8].

3 - Histopathological variables: Malignant/benign, histology, number of resected lesions and tumor size of the largest lesion.

The two groups were well matched except for the size of the largest nodule by imaging (p<0,001).

Short-term post-operative variables were also recorded: hepatic specific complication and general complications stratified according to the Dindo and Clavien classification [9].

For the analysis of bile leak differences, these were defined using the International Study Group for Liver Surgery (ISGLS) Consensus. (3) (**Table 2**).

Table 1. Demographic data of OLR and LLR

Variable	OLR (N=65)	LLR (N=54).	p =
Sex F/M	26/39	24/30	0,625
Age media (range)	58 (24-83)	62 (24-83)	0,110
B.M.I. media (range)	26,6 (18,7-35,8)	26,1 (15,7-34,8)	0,781
ASA (I/II/III/IV)	6/29/29/1	4/26/24/0	0,795
Number of nodule median (SD)*	1,75 (1,14)	1,55 (1,11)	0,221
Size of the biggest nodule in mm media (range)	51,8 (10-230)	31,2 (7-150)	0,007
Bilateral/Unilateral	21/44	10/44	0,088

SD: Standard Deviation
* Number of lesion by imagine

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Table 2. Definition and grades of bile leak (International Study Group for Liver Surgery (ISGLS) Consensus).

Definition	Abdominal drainage fluid with an increased bilirubin concentration (al least 3 times the plasma concentration) beyond the 3rd postoperative day or the need of intervention to treat the biliary collection, or choleperitoneum.
Grade A	Bile leak which does not require or requires a slight change in the clinical management of the patient.
Grade B	Bile leak that requires a change in the clinical management of the patient (additional diagnostic or therapeutic procedures) but without the need for laparotomy. Bile leak which persist for more than 1 week.
Grade C	Bile leak that requires a laparotomy.

From the book “Abdominal surgery complications.How to manage them” Pekolj J et al.

4. Surgical Technique

A standard technique described in the literature was used for OLR.(10) The technique of laparoscopic resections has been described elsewhere.

Although the technique of hepatic transection was the same in both groups, there were different pedicle approaches. The intraglissonian approach for anatomical hepatectomies was the most used in open hepatectomies (83%), while the extraglissonian approach was the most frequently used in the LLR (55%).

In all cases of anatomical hepatectomies for both groups, before performing the resection, an intraoperative cholangiography was performed to know the biliary anatomy, and intraoperative ultrasonography (trans laparoscopic or with conventional transducer) was done to define the vascular anatomy and location of the lesions. In these cases, tests of biliary leakage with contrast, physiological solution or with methylene blue were also performed at the end of the resection. The bilistasia of the cut surface was performed with parenchymal stitches with absorbable suture, in both groups.

During the transection of the liver parenchyma, the central venous pressure (CVP) was maintained lower than 5 mmHg, and the ultrasonic scalpel (Ultrasicion®), cautery and bipolar were the devices used. The crush clamping technique was applied to divide the parenchyma, using titanium or plastic clips (Hemolock®) according to the vessel size. The mechanical suture was only used to section pedicles or large vessels. A silicone drain was systematically left in abdominal cavity.

In the laparoscopic group the pieces were removed with a plastic bag through an umbilical medial incision or through a Pfannestiel incision, or by minilaparotomy if it was a hand assisted procedure.

There were more simultaneous procedures done in the LLR group ($p<0.001$), and the operative time was shorter in LLR (221 min vs 295 min, $p = 0.001$). The length of hospital stay was 6.2 days in the LLR and 11.2 days in the OLR ($p<0.001$).

5. Statistical Analysis

Continuous data are expressed as means with standard deviation (SD) or median with the corresponding range in parentheses. The Mann-Whitney U test was used to compare continuous data, while the X2 test was used for categorical data. Kaplan-Meier test was used to analyze the survival curves, and the log -rank test was used to find the statistically significant differences between them. A p value <0.05 was considered significant. All statistical analyzes were performed using the IBM SPSS Statistic 20.0® statistical software.

6. Results

During the study period, 143 liver resections were performed. Four right hepatectomies of living donor, three trisectionectomies, two resections of lesions located near the confluent of the suprahepatic veins or the vena cava performed by open surgery, and 2 isolated caudate resections, were exclude according to the criteria applied in this study. In the OLR group, 5 patients were excluded, and 1 in the LLR group because they had multiple bilateral liver metastases (more than 5 lesions) in preoperative imaging studies.

Also were excluded for the analysis 6 patients from the LLR group because they were converted to open surgery before finishing the parenchyma transection during laparoscopic time. The causes of conversion were: to assure an R0 resection in 4 cases, and bleeding in the remaining 2, only one of these required transfusion of 2 units of red blood cells (type IIt). It should be clarified that there were no causes of conversion because an intraoperative adverse events type III of the new classification[8].

The study population comprised 119 hepatectomies, 65 OLR and 54 LLR. Table 1 summarizes the demographic and preoperative variables. The only statistically significant difference was the largest nodule size in preoperative imaging studies.

In 20 patients who had a hepatic resection, a simultaneously surgery was performed, 5 in the OLR group and 15 in the LLR group:

- 15 with colectomy (11 LLR group and 4 OLR group).

- 2 with gastrointestinal tract reconstruction (1 LLR group and 1 OLR group).

- 2 LLR with laparoscopic pancreatic resections for neuroendocrine tumors with synchronous liver metastases.

- Finally 1 LLR was performed in conjunction with a laparoscopic cytoreduction for ovarian cancer with implants and single liver metastases.

Of the 54 LLR, 7 were hand assisted from the beginning, and 8 were converted from LLR to hand assisted.

Table 3 summarizes the intraoperative variables. When discriminated by type of hepatectomy, there were no statistically significant differences between the two groups. There were more procedures done simultaneously with LLR group (27% vs 8%, p = 0.004). Differences in operative time were also found (221 min vs 295 min, p = 0.001). No differences were found in the rest of the intraoperative variables.

There were no differences in the number of resected nodules in both groups, nor in histological types.

As in the preoperative images, a larger nodule size was also found in the open group (54mm vs 31.9mm, p = 0.001).

The hospital stay was 6.2 days in the LLR and 11.2 days in the OLR (p = 0.001).

Considering global morbidity, there were fewer complications in the laparoscopic group (27% vs 50%, p = 0.011). Morbidities based on Dindo Clavien classification are detailed in table 5. There were no differences in the proportion of major complications (greater than grade 3). Table 6 shows hepatic complications. Both groups had similar incidences of hepatic complications (bleeding, bile leak, collections and hepatic failure).

There were no overall differences respect bile leak between both groups (ISGLS bile leak A, B and C) (p = 0.450). There were no type C bile leaks in the laparoscopic group. Of the two type C bile leak in the open group, one died at 3 months after multiple endoscopic and surgical interventions. The patient had a right hepatectomy for metastasis of colorectal cancer, was an elderly patient, who presented a lesion of the segment 4 duct that drained to the right bile duct, which was inadvertently sectioned, leaving all segment 4 excluded from the main bile duct. The other patient with type C bile leak was discharged and readmitted with an abdominal fluid collection which needed surgical drainage. The bile leak was resolved after surgery. All type B bile leaks resolved spontaneously postponing withdrawal of abdominal drainage for more than 7 days, or performing percutaneous drainage or with ERCP with stent placement in two cases. In a single case of bile leak of the laparoscopic group, the fistulography showed a segment 6 excluded in a non-anatomical resection of a colorectal metastasis, which was self-limited after 3 months of its percutaneous drainage.

There was one 90-day mortality in the conventional group that was previously detailed.

Table 3. Operative variables.

Variable	OLR (N=65)	LLR (N=54).	p =
AnatHepat /No anat/ Anat+Noanat	29/7/29	20/7/27	0,700
Hepatectomies Brisbane classification: - Central hepatectomy - Right hepatectomy - Right anterior sectionectomy - Right posterior sectionectomy - Left hepatectomy - Left lateral sectionectomy - Segmentectomy - Non anatomic liver resection	1 15[£] 0 2 6 6[£] 5[£] 30	0 4 1 3[¥] 1 8 10[€] 27	0,064
Simultaneous procedure	5/60	15/39	0,004
RFA associated	6/59	3/51	0,450
Operation time.*	295 (100)	221 (DS 121)	0,001
Pringle	28/37	23/31	0,958
Duration of Pringle min.	12,07 (DS 16,9)	14,5 (DS 19,7)	0,683
Transfusion of PRBC	17/48	10/44	0,322
Number of PRBC	0,6 (DS 1,68)	0,5 (DS 1,19)	0,556
Length of hospital stay	11,2 (DS 13,9)	6,2 (DS 7,1)	0,001

[£] Two patients added a non-anatomic liver resection.
[¥] Two patients added a non-anatomic liver resection.
[€] Four patients added a non-anatomic liver resection.

Table 4: Anatomopathological diagnosis.

Variable	Open surgery group (N=65)	Laparoscopic Group (N=54).	p =
Malignant / Benign	55/10	39/15	0,098
Histology **CRM** **MNCNNE** **HCC** **Fibrolamelar** **IH** **Cholangiocarcinoma** **Neuroendocrine Mts.** **Extended cholecystectomy (GB CA)** **HBP Adenocarcinoma** **FNH** **Hemangioma** **Adenoma** **Hydatidcyst** **CaroliDisease** **Othersbenign***	33 8 7 0 2 0 3 1 2 2 2 1 2 2	25 4 2 1 1 3 1 1 3 6 1 2 0 4	0,295
Number of resected lesions	1,7 (DS 1,3)	1,8 (DS 1,5	0,967
Tumor size in mm	54 (DS 48,8)	31,9 (DS 28)	0,001

* Pecoma, hyaline fibrosis, hyaline-vascular fibrosis, regenerationnodule, biliar cyst, AVM.

Table 5. Global morbidity in both groups.

	Complication	Open surgery group N=65	Laparoscopic Group N=54	p=
Complications Yes/ No*		33/32	16/39	0,011
Grade 1	Food intolerance	2	0	
	Wound infection	1	0	
	Bile leak type A	3	3	
Grade 2	Pain€	1	0	
	Pneumonia	5	1	
	Intraabdominal Collection.£	2	0	
	Wound infection	3	0	
	Evisceration	0	1	
	Bile leak type A	1	0	
	Bile leak type B	2	0	
	Fever	0	3	
	PTE	1	1	
	DVT	0	1	
	CVA	1	0	
	Phlebitis	0	1	
Grade 3A	Intraabdominal Collection.¥	5	2	
	Bile leak type B	1	2	
Grade 3B	Bile leak type C	2	0	
	Complicated evisceration	1	1	
	Bleeding	2	0	
Grade 4	Pneumonia	1	0	
	Hollow viscus perforation	1	1	
Complications > 3		13	6	0,188

* If a patient had more than one complication, it counts the most severe one.
€ Pain which required increased analgesia and prolonged hospital stay.
£ Only required ATB treatment.
¥ Required percutaneous drainage.

Table 6. Liver morbidity.

	Complication	OLR N=65	LLR N=54	p =
Liver complication*		12	8	0,117
Bile leak type	A	6	3	
	B	4	3	
	C	2	0	0,656
Bile leak	B y C	6	3	0,450

* Include bile leak

Table 7. Definitions and incidence of bile leak. Modified from Donadon y col[18].

Author	N	Definition of bile leak	%	Year
Belghiti et al	42	Withdrawal of drainage if < 100 ml/day.	4,8	1993
Fong et al	60	Presence of bile in abdominal drainage for more than 1 week.	5	1996
Liu et al	52	Macroscopic evaluation of drainage fluid. Withdrawal of drainage if < 200 ml/day.	3,8	2004
Sun et al	60	Macroscopic evaluation of drainage fluid.	0	2006
Vigano et al	593	Bile leak > 50 ml/day either through an abdominal drainage or the drainage of an intraabdominal collection after the 3^{d} day.	5,7	2008
Kyoden et al	1269	(1) Drainage fluid is clearly bilious (2) bilirubin of drainage is > 5,0 mg / dl in two opportunities or after the 7^{th} day (3) bilious intraabdominal collections and/or bilirubin >5,0 mg / dl.	8,7	2004
Koch et al	70	ISGLS. Bilirubin concentration of abdominal drainage is three times higher the plasma level after the 3^{d} postoperative day or the need to surgically treat a bile collection or choleperitoneum.	16	2011
Rahbari et al	265	ISGLS	27,2	2010
Yamazaki	316	ISGLS	4,4	2102
Guillad et al	1001	(1) Drainage fluid is clearly bilious, (2) bile collection drainage, (3) reoperation because a choleperitoneum.	8	2013
Taguchi et al	241	ISGLS	25,7	2015
Brooke-Smith et al	603	ISGLS	11	2014
Donadon et al	475	Drainage bilirubin >10 mg / dl in two or more consecutive screenings. These ones took place systematically in the 3^{d}, 5^{th}, and 7^{th} postoperative day.	8,2	2016

7. Discussion

Bile leak is one of the most frequent complications in hepatectomies and is one of the main causes of major morbidity and mortality due to sepsis in these procedures. In the consensus meeting held in Marioka - Japan in 2014, there was some question regarding a possible higher rate of bile leaks in LLR[4].

Trying to answer this question implies a methodological challenge. First, there is a great heterogeneity of definitions of bile leak in the literature. This leads to the large variation in incidence in different studies, as shown in Table 7. This is equally observable in our results. If we use other definitions such as the one used by Vigano et al. [10], where bilirrhage was defined as drainage flowing more than 50 ml / day of bilious fluid, the incidence we find in our series is half of that reported as "global bilirrhage", including type A bile leak, which do not require changes in postoperative management. On the other hand, when they are included, there is doubt about the clinical relevance of measuring them. This concept is also extensible to the definition of "biliary fistula" which makes relevance to that bilirrhage that is perpetuated in time. This definition encompasses a very small group of patients with bilirrhage, so we conclude that this term should not be used interchangeably.

Among other possible biases, in addition to the sample size, is case selection. As a retrospective study, there could be the bias of indicating open surgery to the most difficult cases. The increased tumor size of the nodules in the open group is noteworthy, although the difference in 2 cm should not have influenced the results. Therefore, we excluded all patients with complex hepatectomies, as well as those requiring biliodigestive anastomosis. Similarly, another possible bias occur when laparoscopic or open techniques are not homogeneous in the type of parenchymal transection. We believe that one of the strengths of our study is that both groups were performed with the same technique.

Table 3 presents the different hepatectomies performed in each group. There are also difficulties in definitions since the simple classification of minor hepatectomy (less than two resected segments) and major hepatectomy (more than two resected segments) is different if they are applied for open or laparoscopic surgery, as defined in the 1st Louisville Consensus in 2008 [11, 12], which include right sectionectomies (i.e. two segments) within major hepatectomies. Therefore, we decided to present the complete list of liver resection according to the Brisbane classification performed in both groups. It was not possible to separate the groups according to the presence of risk factors for bilirrhage, since there was great controversy when quantifying them. A recent meta-analysis has indicated a higher risk in: previous hepatectomy, anatomic resections, major hepatectomy, right anterior sectionectomy, left trisectionectomy, central sectionectomy, transfusions, operative time, resections with biliodigestive reconstructions, and isolated resection of segments 1, 2 and 5[2]. However, there are publications that have found other different factors, such as non-anatomical resections, previous treatment with Bevacizumab, two-stage hepatectomy, selective pedicle clamping time, R1 or R2 resections, and failure to perform[13, 14]. Also male[13], BMI [5], preoperative white blood cell count [15], as well as albumin levels and test results with green of indocyanine[16], among others. This large heterogeneity of risk factors prevented the application of a score to compare groups.

Regarding the postoperative results, some advantages of laparoscopic technique such as shorter operative time, lower morbidity and hospital stay, are presented in our study. Although these were not objectives, they reflect the findings of other investigations such as that of Oslo-CoMet [17], which is the only prospective randomized study conducted to date.

With respect to bile leak, our manuscript is the first one that specifically focuses on comparing them between the two approaches, with the same technique of liver transection. We did not find differences in incidence in both groups, ie, in the global numbers (bile leak type A, B and C) and in the major bile leak (bilirrhage B and C). These findings were expected since the same technique was used to transect the parenchyma regardless of the type of approach.

We believe that these results, which should be corroborated by randomized prospective studies, offer some evidence to the concern raised in the Marioka consensus. It also reaffirms the postulate for any laparoscopic intervention, which is to reproduce the same techniques used in the open approach.

8. Conclusion

Using the same form of parenchymal transection, the type of approach did not increase the incidence of bile leak in our cases.

9. Acknowledgment

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