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Laparoscopic Simultaneous Approach of Colorectal Cancer with Liver Metastases has Higher Morbidity and Length of Hospital Stay than Isolated Laparoscopic Liver Resection

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1. Abstract

When colorectal liver metastases (CRLM) present synchronously with the primary tumor, it is controversial whether to perform a simultaneous or sequential laparoscopic approach of both.

1.2. Objective: To compare the morbidity and mortality of the Simultaneous Laparoscopic Approach. (SLA) of CRLM and the primary tumor compared with isolated Laparoscopic Liver Resection (I- LLR).

1.3. Methods: All LLR of suspected CRLM were included. Two groups were compared: 'SLA group' (colon and liver) versus 'I-LLR group' (only liver). Preoperative and intra operative variables were analyzed, short and long outcomes.

1.4. Results: From 08/2008 to 11/2018, 60 LLR were performed on suspected CRLM: 21 were in the 'SLA' group and 39 in the 'I-LLR' group. There were no differences in the diameter and number of nodules resected. The overall morbidity was 43% with no mortality. The SLA group presented a morbidity of 71.4% compared with 25.6% for the I-LLR (p = 0.0048). However, the rate of major complications (≥3b) was similar (4.7 vs 2.5%, p=0.65). The length of hospital stay (LOS) was 11 and 6 days, respectively (p=0.002).

1.5. Conclusion: The simultaneous approach has higher morbidity and LOS, although the rate of major complications was similar. SLA should be advocated for selected patients.

2. Introduction

Colorectal Cancer (CRC) is a leading cause of tumor-related morbidity and mortality worldwide [1]. One every six patients with colon cancer presents with synchronous Colorectal Liver Metastases (CRLM) [2], but it is not clear if it is an accurate data because different definitions of synchronous CRLM exist [3]. The optimal timing of resection of the primary and metastatic disease is unclear, as there are no randomized trials in this setting. Not having a clear definition and the absence of strong evidence leaves the synchronous CRLM without a unique standard approach.

Some published series have demonstrated the feasibility, safety, and efficacy of Open Synchronous Resections (OSR), with acceptable morbidity and mortality [4]. Assuming similar long-term outcomes compared with the sequential approach, the Synchronous

Resection (SR) may offer several potential benefits for patients: shorter Length of Hospital Stay (LOS), reduced costs, and only one major operation. However, the disadvantages of the simultaneous approach include longer operating times, which may increase major postoperative complication rates.

Since the laparoscopic approach seems to have less morbidity, is this a reason to promote the simultaneous approach of SCRLM with the primary? There are randomized controlled studies that confirm the benefit of the laparoscopic approach in colorectal as liver surgery individually, but there are not in simultaneous laparoscopic resection [5]. There are data of simultaneous laparoscopic approach coming from small case series, most of them are initial experiences, as well as comparative studies between simultaneous laparoscopic approach versus conventional approach, meta-analysis and paired match analysis [6-10]. In general, the conclusions are that in selected cases, it is feasible and safe, showing benefits in terms of hospital stay mainly. Still, the data supporting simultaneous resection are limited, retrospective and with selection bias.

Nevertheless, there is potential bias when comparing postoperative morbidity between a simultaneous approach (two interventions) and a single one (two sequential procedures). It is logical to conclude that a simultaneous approach would be associated with higher morbidity (two combined interventions) but a shorter total length of hospital stay (LOS).

The objective of this study is to compare the morbidity, mortality and LOS of the SLA of CRLM and the primary tumor compared with the isolated laparoscopic liver resection (sequential approach).

3. Methods

From August 2008 and February of 2019, 101 consecutive LLR were performed at the Hepatobiliary-pancreas and Liver Transplant Unit of Hospital Británico de Buenos Aires – Argentina. Data from these procedures were prospectively collected in a database and were retrospectively reviewed. ‘Synchronously detected liver metastases’ was defined as the CRLM detected at or before the diagnosis of the primary tumor [3]. In this is intention to treat analysis, 60 patients were included with radiologic imaging of suspected CRLM and divided into two groups: ‘Simultaneous Laparoscopic Approach’ (SLA), defined as the resection of the liver and colon tumors at the same surgical intervention, and the ‘Isolated-Laparoscopic Liver Resection’ (I-LLR), defined as the resection of only the liver metastases as part of a sequential approach (colon first or in a second intervention). The process of selecting candidates for combined resections was evaluated by a multidisciplinary team. The complicated primary tumor (obstruction or perforations) and the need of multivisceral resection of the primary were considered contraindication of SLA. The simultaneous procedures were performed by two separates teams (colorectal surgeon and hepatobiliary surgeon).

4. Variables

The following variables were analyzed. The preoperative variables: demographic data; number, location, and size of the largest lesion in the liver at diagnosis; and location of colorectal cancer. Surgical variables: type of liver resection, time of surgery, pedicular clamping, intraoperative events, blood loss, conversion rate, and resection margin. Short term variables: specific, overall morbidity and perioperative mortality, length of hospital stay, and pathological variables. The specific morbidity was divided into ‘specific colorectal’, ‘specific liver’, and ‘global’; given the fact that I-LLR group had no colorectal interventions, there were specific colorectal complications registered only in the SLA group and there wasn´t compared between the groups.

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

There were 21 patients in the SLA group and 39 in I-LLR group. Patient demographics and clinical data are listed in (Table 1). In the I-LLR were enrolled more ASA 3 patients (49%) than in the SLA group (14%). There were more lesions in the I-LLR (median of 2 vs 1 of the SLA, p = 0.02), and many of them located in the non-laparoscopic liver segment (I-LLR 72% vs SLA 47%, p = NS). In the I-LLR ten major Hepatectomy (25.2%) were performed compared with none in the SLA (p = 0.02) (Table 2).

In the SLA there was a longer operation time, with more need of transfusion and conversions to open surgery (Table 3). Five patients in the SLA were converted during the liver procedure and were in the first half of the experience. Eight of the nine transfused patients in the SLA group were at the learning curve (before the first 50 cases of LLR).

The length of hospital stay was longer in the SLA (median 11 days’ vs 7 I-LLR, p = 0.03), and the overall morbidity was higher in the SLA (SLA 71.4% vs I-LLR 30.8%, p < 0.01). The specific liver morbidity had the same rate (SLA 19% vs I-LLR 17.9%, p = NS). The major morbidity (> grade 3B), had also the same rate (SLA 28.6% vs I-LLR 15.4%, p = NS). There was a significant difference in the Grade 2 complications (SLA 38.1% vs I-LLR 5.1%): Deep Vein Thrombosis, incisional hernia, pneumonia, unexplained fever, biliary leak types A and urinary tract infection (Table 4).

Table 1: Demographic and clinical characteristic

Variable	SLA n = 21	I-LLR n = 39	p =
Age (years), median (range)	62 (34 – 78)	64 (33 – 83)	0.33
Sex (female/male)	9/12	14/25	0.59
BMI (kg/m^2), median (range)	25.9 (19.6-36.7)	25.9 (17.1 – 34.8)	0.83
ASA I/II/III	0/18/3	2/18/2019	0.01
Neoadjuvant chemotherapy, n (%)	4 (20)	18 (48.6)	0.03
Number of lesions*, median (range)	1 (1 – 3)	2 (1 – 4)	0.02
Multiple lesions (> 5) (%)	2 (9.5)	4 (10.2)	0.92
Larger diameter at diagnosis mm*, median (range)	20 (7 – 88)	25 (7 – 90)	0.25
Bilobar, n (%)	5 (28.6)	16 (25.6)	0.8
Location of SLMs (n) (%)			
Laparoscopic segment: S1, S2, S3, S4b, S5, S6	11 (52.4)	11 (28.2)	0.06
Non laparoscopic segment: S7, S8	10 (47.6)	21(71.8)	
R1 resection (%)	0	2(5.1)	0.88

ASA: American Society of Anesthesiologists classification. BMI: Body Mass Index

Table 2: Type of liver resection

Variable	SLA n = 21	I-LLR n = 39	p =
Liver resection	5 (23.8)	16 (41)	
Anatomical, n (%)	15 (71.4)	17 (43.6)	
Non anatomical, n (%)	1 (4.8)	6 (15.4)	0.10
Anatomical – Non Anatomical, n(%)			
Liver resection (Brisbane)	15 (71.4)	17 (43.6)	
A typical resection, n (%)	3 (14.3)	7 (17.9)	
Segmentectomy, n (%)	0	1 (2.6)	
Bi segmentectomy, n (%)	3 (14.3)	4 (10.3)	
Left lateral sectionectomy, n	0	3 (7.7)	
(%) Right posterior	0	2 (5.1)	
seccionectomy Left	0	5 (12.8)	0.07
hepatectomy			
Right hepatectomy, n (%)			
Major hepatectomy (> 2 liver segments) †, n (%)	0	10 (25.6)	0.02

† Including Right Posterior Seccionectomy

Table 3: Surgical Variables

Variable	SLA n = 21	I-LLR n = 39	p =
Totally laparoscopic, n	19 (90.5)	39 (100)	0.22
(%) Hand-assisted, n (%)	2 (9.5)	0	
Conversion to open surgery, n(%)*	5 (23.8)	0	< 0.01
Associated RFA, n (%)*	2 (9.5)	1 (2.6)	0.57
Pringle maneuver, n (%)	14 (66.7)	21 (53.8)	0.33
Operative time min., median (range)	375 (240 – 720)	280 (112 – 510)	< 0.01
Liver resection time min. ,			
Number of patient transfused, n (%)	9 (42)	4 (10.3)	< 0.01

Table 4: Short term variables

Variable	SLA n = 21	I-LLR n = 39	p =
Length of hospital stay days, median (range)	11 (3 – 49)	7 (3 – 37)	0.03
Mortality, n (%) (grade 5)	0	0	-
Overall morbidity, n (%)	15 (71.4)	12 (30.8)	<0.01
Grade 1	1 (4.8%)	2 (5.1%)	
Grade 2	8 (38.1%)	2 (5.1%)	
Grade 3A	5 (23.8%)	5 (12.8%)	
Grade 3B	0	1 (2.6%)	
Grade 4	1 (4.8%)	0	
Colorectal morbidity, n (%)	4 (19)	-	-
Leakage, n	3	-	-
Liver morbidity, n (%)	4 (19)	7 (17.9)	0.9
Abdominal collection, n	2	3	
Bile leak, n	2	4	
Global morbidity, n (%)	7 (33.3)	5 (12.8)	
Bowell perforation, n	1	0	
Deep Vein Thrombosis, n	1	1	
Incisional hernia, n	1	1	
Pneumonia, n	1	1	
Unexplained fever, n	1	2	
Vomit	1	0	
Urinary tract infection, n	1	0	

7. Discussion

Nowadays it still the debate was to perform simultaneous or sequential approaches in synchronous CRLM. There are many publications in open surgery and a new randomized clinical trial recruiting patients but still ongoing [11] Simultaneous or delayed hepatectomy for synchronous colorectal liver metastases, this is the dilemma (period) It is well known the benefit of simultaneous approach in very selected cases in open surgery, but there is doubt whether this results can be reproduced with laparoscopic surgery. [3, 4].

The objective of our study was to answer the question of whether a simultaneous approach can benefit the postoperative course of these patients. This brings important design challenges. It is difficult to compare a group of cases with two simultaneous interventions (liver and colon) with another performing only one (only liver). Besides, it was relevant to compare the results of morbidity related to the hepatectomy in both groups that were subphrenic/perihepatic abscesses, bile leak/biloma, and transient hepatic insufficiency.

The bias of this study is not only the retrospective design with clear selection bias but also the small number and not matching groups and the long period of the study, a well-known bias of the cancer studies since the chemotherapy regimens change over the time. This last bias was the reason to not include oncological results.

In our study, it was expected to have higher morbidity rates in the I-LLR since this group had sicker patients and a higher rate of major hepatectomies. However, the SLA group cases were associated with higher overall morbidity, conversions, need for transfusion, longer operative times and length of hospital stay.

This worst outcome in the very selected SLA group requires to separate this finding in two categories. On one side, the results of combining two interventions are logical, for example, the surgical time and LOS. However, by other side, there are paradoxical results of worst morbidity rates in the group of easier liver resections patients (SLA). Whether the longer pneumoperitoneum time affects these overall results are a potential cause but requires further analysis.

The results of most recent reports of series of simultaneous laparoscopic approaches (Table 5) have the same selection criteria: few and small lesions to perform the simultaneous approach, which means less extended liver resections, and exclusion of the complicated primary tumor or the need of multivisceral resection. Comparing our results with the reported data, the operative time and length of hospital stay were similar but the overall morbidity was higher compared with other series (71% overall morbidity), in particular, morbidity grade 2 (pneumonia, pleural effusion, atrial fibrillation, etc.). These findings were similar to recently published data coming who reported 58% of overall morbidity and 23.5% grade 2 morbidity, which means a high number of grade 2 morbidity compared with other published series One possible cause of a higher number of morbidity grade 2 could be related to the longer operation time. Having a pneumoperitoneum for more than four hours have more incidence of respiratory complication, and it is a risk factor of deep vein thrombosis or pulmonary embolism.

Table 5: Case series of simultaneous approach

Author	N	CRLM size, cm	No. of CRLM, median	Minor LLR	Operative time, min (range)	Conver. rate, %	Complic (%)	Hospital stay (days)
Lee et al (2010)	10	3.9±2	N/a	9 (90%)	401 (230-620)	1 (10)	1 (10)	10.5 (7-15)
Polignano et al (2012)	13	N/a	N/a	13 (100%)	370 (190-540)	0	3 (23)	7 (3-54)
Spampinato et al (2013)	5	3.4 (2.3-5)	4 (3-7)	0 (0%)	495 (380-510)	0	1 (20)	6 (5-8)
Berti et al (2015)	35	4 (0.4-8.5)	N/a	30 (86%)	240 (120-450)	0	7 (20)	8 (4-30)
Ratti et al (2015)	25	2.9 (0.5-11)	2 (1-6)	19 (76%)	420 (170-720)	0	6 (24)	9 (4-17)
Present study (2019)	21	20 (0.7- 8.8)	1 (1 – 3)	21 (100%)	375 (240 – 720)	5 (23.8)	15 (71)	8 (3 – 49)

This is the third published series in terms of the number of laparoscopic simultaneous resection of the primary with CRLM (Berti et al 35 cases, Ratti et al 25, and ours 21 cases). The lack of worldwide acceptance of the simultaneous approach is reflected in recently published the NSQIP data: only 21 cases in all United States were synchronous laparoscopic resection of colorectal and liver metastases. Our study reflects that there is more experience to advocate this procedure out of strong selective criteria.

There is obvious bias when comparing these two different approaches (one against two procedures), but the advantage finds it of the simultaneous approach in open surgery (one procedure, shorter LOS, lower cost, etc.) probably it is not the same for the laparoscopic approach. Further studies and randomizes studies will need to corroborate the results of our study.

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