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ORIGINAL ARTICLE

Laparoscopic Versus Open Major Hepatectomy: Analysis of Clinical Outcomes and Cost Effectiveness in a High-Volume Center

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Abstract

Background Considering the increasing evidence on the feasibility of laparoscopic major hepatectomies (LMH), their clinical outcomes and associated costs were herein evaluated compared to open (OMH).

Methods Major contributors of perioperative expenses were considered. With respect to the occurrence of conversion, a primary intention-to-treat analysis including conversions in the LMH group (ITT-A) was performed. An additional per-protocol analysis excluding conversions (PP-A) was undertaken, with calculation of additional costs of conversion analysis.

Results One hundred forty-five LMH and 61 OMH were included (14.5% conversion rate). At the ITT-A, LMH showed lower blood loss ($p < 0.001$) and morbidity (global p 0.037, moderate p 0.037), shorter hospital stay (p 0.035), and a lower need for intra- and postoperative red blood cells transfusions ($p < 0.001$), investigations (p 0.004), and antibiotics (p 0.002). The higher intraoperative expenses (+ 32.1%, $p < 0.001$) were offset by postoperative savings (− 27.2%, p 0.030), resulting in a global cost-neutrality of LMH (− 7.2%, p 0.807). At the PP-A, completed LMH showed also lower severe complications (p 0.042), interventional procedures (p 0.027), and readmission rates (p 0.031), and postoperative savings increased to − 71.3% (p 0.003) resulting in a 29.9% cost advantage of completed LMH (p 0.020). However, the mean additional cost of conversion was significant.

Conclusions Completed LMH exhibit a high potential treatment effect compared to OMH and are associated to significant cost savings. Despite some of these benefits may be jeopardized by conversion, a program of LMH can still provide considerable clinical benefits without cost disadvantage and appears worth to be implemented in high-volume centers.

Keywords Laparoscopic liver resection · Major hepatectomies · Financial costs · Conversion

Abbreviations

LMH	Laparoscopic major hepatectomies
OMH	Open major hepatectomies
PP-A	Per-protocol analysis
ITT-A	Intention-to-treat analysis
ICU	Intensive care unit
USD	United States dollar
FFP	Fresh frozen plasma
RBC	Red blood cells

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Introduction

The laparoscopic approach for liver surgery has developed progressively and cautiously over the last years.[1–9] Despite increasingly reported, laparoscopic major hepatectomies are still uncommon procedures and their diffusion keeps restricted to few high-volume centers, with the open technique remaining the worldwide standard.[10–14] Among factors limiting their spread, a potential barrier to their diffusion is their uncertain effect on financial costs. The issue was addressed during the Second International Consensus Conference on Laparoscopic Liver Resections held in 2014.[15] At that time the evidence available on the topic was clear as for what concerns minor laparoscopic liver resections, which were globally evaluated as cost-effective procedures when compared to open. Indeed, a consistent number of studies reported that the considerable intraoperative expenses associated with the minimally invasive approach resulted greatly counterbalanced by postoperative cost-savings and have favored their implementation by health care systems.[16–21] On the contrary, the data concerning the financial impact of a laparoscopic approach for major liver resection were deemed insufficient to draw final conclusions. An insight on the cost implications of laparoscopic major hepatectomies appears worth considering the high complexity of these procedures. Thus, specific evidence is desirable for a comprehensive understanding of their profile of efficacy before promoting their diffusion on a large scale.

Notably, it has recently been demonstrated that conversion to open may reduce the benefits related to a minimally invasive technique, providing patients a perioperative course approaching that of open liver resections.[22,23] As such—beyond the clinical effect—the occurrence of conversion is expected to have a financial impact also, but this remains unexplored yet.

The aim of this study is to compare both clinical outcomes and costs of laparoscopic versus open major hepatectomies carried out in a high-volume center, with reference to the costs associated with conversion to open. The ultimate goal is to elucidate comprehensively the effect of a laparoscopic liver surgery program that includes complex procedures as major hepatectomies, and to clarify its value in the actual clinical practice.

Methods

Study Design

A prospectively collected single-center database of consecutive patients undergoing liver resections (January 2005 to November 2017) at the Hepatobiliary Surgery Division of San Raffaele Hospital, Milan, was reviewed. Patients undergoing laparoscopic major hepatectomies were identified and considered as the study group (LMH). Patients undergoing open major hepatectomies (OMH) during the same period were selected as the control group. According to the Brisbane 2000 Nomenclature, major liver resections were defined as the resection of three or more liver segments.[24]

Major hepatectomies associated with bile duct resection and reconstruction were excluded since predominantly carried out for Klatskin tumors, considering the clinical peculiarities in the perioperative outcomes of these patients. Also, the analysis was restricted to a 3-year time frame (November 2014–November 2017), in order to reduce the influence of major variations in the inflation power over time on final results (mean annual inflation rate according to the Italian National Statistical Institute: 2014 + 0.2%; 2015–0.1%; 2016–0.1%; 2017 + 1.1%), and to consider a homogeneous pool of procedures carried out with a standardized technique and perioperative management.

With respect to the occurrence of conversion to open during laparoscopic resections, the primary analysis relied on the intention-to-treat principle (ITT-A, i.e., retaining the converted cases in the laparoscopic group) in order to reflect at best the real clinical setting, where conversion is required in a variable proportion of patients. The results of a secondary analysis were also reported considering the data according to the per-protocol principle (PP-A, i.e., excluding the converted cases, thus including laparoscopically completed procedures only in the LMH group). This allowed to provide complementary information on the full potential treatment effect of the minimally invasive approach, and to calculate the average cost of conversion of LMH.[25]

Routine blood tests, computed tomography of the abdomen with triphasic liver contrast enhancement and/or liver-specific contrast magnetic resonance imaging were performed in all patients and discussed at multidisciplinary hepatobiliary meetings. The indication for major hepatectomy was decided without adjustments based on the surgical approach (laparoscopic/open). The following disease characteristics were considered as exclusion criteria for a laparoscopic approach (i.e., criteria for allocation to the open technique d'emblée) over the entire period: lesions strictly adjacent or infiltrating the hepatocaval confluence or inferior vena cava; lesions with presumed infiltration of the hepatic vein of the future liver remnant; repeated hepatectomy after previous open liver resection; patients with portal vein thrombosis requiring portal vein thrombectomy. In addition, from April 2015 onwards, those patients elected to hemihepatectomy were randomized to the open or laparoscopic approach in the context of the Orange 2 Plus prospective randomized controlled trial of laparoscopic versus open hemihepatectomies.[26] Only pure laparoscopic resections were attempted. Our technique for laparoscopic and open major hepatectomies has been already described.[10]

Endpoints and Definitions

Intra- and perioperative outcomes were analyzed for the assessment of feasibility and efficacy. Intraoperative outcomes included: operative time (minutes), blood loss (mL), red blood cells and fresh frozen plasma transfusions, completeness of resection (R0), conversion to open (for LMH group), and reasons for conversion. Postoperative outcomes included 30-day mortality and morbidity (general and liver-specific), reoperation, 30-day readmission, blood products (red cells and fresh frozen plasma) transfusions, postoperative investigations (laboratory, endoscopic/radiological), administration of medical agents, postoperative radiological/endoscopic procedures (including radio-guided drainage of collections, ascites or pleural effusion; endoscopic retrograde cholangiopancreatography ± insertion of biliary stent), length of stay (days). The severity of morbidity relied on the Accordion Classification.[27] Specific definitions of liver complications were adopted: liver failure as an increased international normalized ratio and concomitant hyperbilirubinemia on or after postoperative day 5;[28] ascites as an abdominal drainage above 10 mL/kg body weight/day after postoperative day 3;[29] bile leak as a bilirubin concentration in the drainage above three-fold of serum total bilirubin on or after pod 3, or the need for radiologic or operative intervention from a biliary collection or bile peritonitis.[30] Resection margins were defined into R0 and R1.[31]

The financial analysis took into consideration various contributors of hospital costs (investigations and clinical evaluations in the setting of the preoperative assessments were excluded). Intraoperative expenses included operating room charges per minute, equips (surgeons, anesthetist, nurses) per minute, disposable devices per piece, sterilization/maintenance of reusable devices, anesthetic medical agents per posological unit, blood transfusion requirements per unit, histopathological exam (frozen sections and final) per service. Postoperative costs included blood transfusion requirement per unit, drugs requirements (analgesics, antibiotics, diuretics, albumin, deep vein thrombosis prophylaxis) per posological unit, laboratory testing per service, postoperative imaging per service, any reintervention (radiological and/or surgical) per service, and ward/ICU bed per night. Any readmission by 30 days from discharge was considered. The calculation of costs for each patient was based on a uniform nominal price of individual items; the tariffs agreed between our hospital and the companies on January 2016 were considered as the source of cost data. All costs calculations were performed in Euro, and results expressed in both Euro and United States Dollar (USD) (January 2016 exchange rate 1.00 Euro = 1.0859 USD). The average cost of conversion for LMH was calculated as mean cost of converted LMH − mean cost of completed LMH.

Prior to the comparison, relevant variables were also analyzed to test the homogeneity between the two groups.

Statistics

Statistical analysis was performed through SPSS ver. 22 (SPSS Inc., Chicago, IL, USA). For continuous variables, median values with interquartile ranges were considered since their distribution was skewed (Shapiro-Wilk Test); categorical variables were expressed as absolute values and proportions. Continuous variables were compared using the non-parametric Mann-Whitney test; categorical variables were compared through the Fisher's exact or chi-square test. Continuous variables related to costs are expressed as means ± standard deviations (SD), absolute difference, percentage difference, and compared between groups using Student's *t* test. Statistical significance was set at $p < 0.05$ and hypothesis tests were two-sided.

Results

Intention-to-Treat Analysis

Two hundred and six patients within the study period were identified (145 LMH and 61 OMH).

The proportion of benign and malignant diagnoses within the laparoscopic and open group was different (*p* 0.032). However, no significant differences were recorded between the two groups in terms of specific histological diagnoses, baseline characteristics, and type of procedures (Table 1).

Twenty-one patients in the laparoscopic group were converted to open (14.5%). The commonest reason was a concern of oncologic inadequacy (8 patients, 38.1%). Other reasons were bleeding (6 patients, 28.6%), technical impossibility to proceed (3 patients, 14.3%), impossible adhesiolysis as needed (3 patients, 14.3%), and the concern of contamination in a patient affected by hydatid liver disease (1 patient, 4.8%).

Perioperative Outcomes

Perioperative outcomes are depicted in Table 2.

Despite longer operative time (*p* 0.040), LMH were associated with lower blood loss ($p < 0.001$), lower intraoperative blood product transfusions (RBC $p < 0.001$; FFP *p* 0.001), lower postoperative morbidity (*p* 0.037) with significant reduction in both general, and liver-specific complications (*p* 0.029 and *p* 0.035), in particular, infectious complications and postoperative ascites (*p* 0.003 and *p* 0.029). When stratified for severity, moderate morbidity was found significantly reduced in the laparoscopic group (*p* 0.037), along with a shorter postoperative total stay (*p* 0.035). Laparoscopic patients showed a significantly lower need for radiological investigations (*p* 0.004), medications (diuretics *p* 0.002, antibiotics *p* 0.037), and RBC transfusions ($p < 0.001$).

Costs

For LMH, the expenses related to both surgical devices and theater usage/dedicated equipe were significantly higher than OMH and justified the globally higher intraoperative costs (+ 32.1%, $p < 0.001$) (Table 3). On the other hand, a 27.2% reduction in postoperative costs was seen for LMH (*p* 0.030), sustained in particular by a significant decrease in expenses for medical agents and blood products. As a result, the balance between intra- and postoperative expenses turned into a total

Table 1 Baseline characteristics and type of liver resections performed in the LMH and OMH group

	OMH $n = 61$	LMH $n = 145$	p value*
Diagnosis, n (%)			
Benign/malignant	5/56 (8.2/91.8)	30/115 (20.7/79.3)	0.032
Hepatolithiasis	2 (3.3)	7 (4.8)	0.564
Hydatid disease	1 (1.6)	3 (2.1)	>0.999
Hemangioma	–	10 (6.7)	0.092
Focal nodular hyperplasia	–	3 (2.1)	0.130
Other benign	2 (3.3)	7 (4.8)	0.665
HCC	21 (34.4)	47 (32.4)	>0.999
Intrahepatic cholangiocarcinoma	9 (14.7)	23 (15.9)	0.871
CRC metastases	18 (29.5)	40 (27.6)	0.937
Other	8 (13.1)	5 (3.4)	0.072
Malignant primary/secondary, n (%)	30/26 (53.6/46.4)	89/56 (61.4/38.6)	0.250
Age (years)	67 (62.5–74)	67 (51.5–77.75)	0.720
Gender, n (%)			
Female	22 (36.1)	65 (44.8)	0.537
Male	39 (63.9)	80 (55.2)	
ASA Score, n (%)			
1	–	12 (8.3)	0.256
2	35 (57.4)	82 (56.6)	
3	25 (41.0)	51 (35.2)	
4	1 (1.6)	–	
Size of the biggest lesion (mm)	69 (48.5–140.5)	64 (46.5–115)	0.238
Background liver, n (%)			0.440
Healthy	32 (52.4)	82 (56.5)	
Steatosis	9 (14.7)	27 (18.6)	
Fibrosis/cirrhosis	20 (32.8)	36 (24.8)	
Portal hypertension, n (%)	2 (3.1)	9 (6.2)	> 0.999
Child-Pugh grade, n (%)			0.375
A	19 (95.0)	36 (100)	
B	1 (5.0)	–	
Previous abdominal surgery, n (%)	31 (50.8)	65 (44.8)	0.676
HPB surgery	20 (32.8)	43 (29.6)	0.285
Laterality of the hepatectomy, n (%)			0.639
Left hemihepatectomy/trisectionectomy	26 (42.6)	59 (40.7)	
Right hemihepatectomy/trisectionectomy	35 (57.4)	86 (59.3)	
Associated hilar lymphadenectomy, n (%)	8 (13.1)	17 (17.7)	0.120

*The distribution of dichotomous categorical variables is expressed by percentages (absolute frequency). Continuous variables are expressed as median (interquartile range)

Legend: HCC, hepatocellular carcinoma; CRC, colorectal cancer; ASA score, American Society of Anaesthesiologist score; HPB, hepatopancreatobiliary

cost-neutrality of LMH when compared to their open counterpart (− 7.2%, p 0.807).

Per-protocol Analysis and Costs of Conversion

The per-protocol analysis compared 124 completed LMH with 61 OMH.

Perioperative Outcomes

Perioperative outcomes are depicted in Table 4.

Completed LMH were associated with longer operative time (p 0.047), lower blood loss ($p < 0.001$), lower intraoperative blood product transfusions (RBC $p < 0.001$; FFP p 0.001). Completed LMH also exhibited a lower postoperative morbidity rate (p 0.003) with significant reduction

Table 2 Comparison of perioperative outcomes between LMH and OMH groups within an intention-to-treat analysis

	OMH $n = 61$	LMH $n = 145$	p value*
Intraoperative outcomes			
Operative time (min)	275 (215–325)	310 (245–355)	0.040
Blood loss (mL)	950 (550–1300)	425 (300–750)	< 0.001
Red blood cells transfusion, n (%)	23 (37.7)	19 (13.1)	< 0.001
Fresh frozen plasma transfusion, n (%)	16 (26.2)	–	0.001
R0 resection, n (%)	55 (90.2)	132 (91.0)	0.244
Postoperative outcomes			
Morbidity, n (%)	19 (31.1)	34 (23.4)	0.037
Severity of morbidity, n (%)			
Mild	2 (3.2)	4 (2.7)	0.194
Moderate	13 (21.3)	23 (15.9)	0.037
Severe	4 (6.5)	7 (4.8)	0.200
Liver-specific complications, n (%)	23 (37.7)	24 (16.5)	0.035
Liver failure	3 (4.9)	5 (3.4)	0.886
Ascites	11 (18.0)	10 (6.9)	0.003
Collection	5 (6.5)	4 (2.7)	0.425
Cholangitis	2 (3.2)	5 (3.4)	0.465
Bile leak	1 (1.6)	–	0.234
Portal vein thrombosis	1 (1.6)	–	0.465
General complications, n (%)	19 (31.1)	22 (15.2)	0.029
Hemorrhage	1 (1.6)	–	0.445
Ileus	1 (1.6)	5 (3.4)	0.229
Chest infection	5 (6.5)	6 (4.1)	0.298
Cardiovascular	5 (6.5)	4 (2.7)	> 0.999
Urinary	2 (3.2)	4 (2.7)	> 0.999
Pancreatitis	1 (1.6)	3 (2.1)	> 0.999
GI bleeding	3 (4.9)	–	0.238
Other	1 (1.6)	–	0.445
Infectious complications, n (%)	13 (21.3)	13 (9.0)	0.029
Death, n (%)	1 (1.6)	1 (0.7)	> 0.999
Reoperation, n (%)	2 (3.2)	2 (1.4)	> 0.999
Readmission, n (%)	8 (13.1)	6 (4.1)	0.462
Total stay (days)	7 (6–7)	6 (6–7)	0.035
Radiological imaging, n (%)	31 (50.8)	23 (15.9)	0.004
Antibiotic therapy, n (%)	34 (55.7)	43 (29.6)	0.037
Albumin, n (%)	10 (16.4)	15 (10.3)	0.667
Diuretics, n (%)	39 (63.9)	32 (22.1)	0.002
Red blood cells transfusion, n (%)	34 (55.7)	17 (11.7)	< 0.001
Fresh frozen plasma transfusion, n (%)	19 (31.1)	16 (11.0)	0.060
Radio-guided or endoscopic procedures, n (%)	14 (22.9)	16 (11.0)	0.074

*The distribution of dichotomous categorical variables is expressed by percentages (absolute frequency). For continuous variables, values are expressed as median (interquartile range)

in both general and liver-specific complications (p 0.015 and p 0.020), in particular, infectious complications and postoperative ascites (p 0.013 and p 0.002). When stratified for severity, both moderate and severe morbidity were found significantly reduced in the laparoscopic group (p 0.005 and p 0.042), along with a shorter postoperative total stay (p 0.003) and also lower readmission rates (p 0.031). Laparoscopic patients showed a lower need for radiological investigations (p 0.003), medications (diuretics $p < 0.001$, antibiotics p 0.038, and also albumin p 0.015),

Table 3 Comparison of intra-, postoperative, and total costs between LMH and OMH groups within an intention-to-treat analysis

	OMH $n = 61$	LMH $n = 145$	Absolute difference	% difference	p value*
Theater usage and dedicated equipe	1371 (± 380)	1540 (± 333)	+ 169	+ 10.9%	0.030
	1489 (± 412)	1672 (± 361)	+ 183		
Reusable devices	288 (± 41)	378 (± 50)	+ 90	+ 23.8%	< 0.001
	313 (± 44)	410 (± 54)	+ 97		
Disposable devices	820 (± 313)	1790 (± 291)	+ 970	+ 54.2%	< 0.001
	890 (± 339)	1944 (± 315)	+ 1054		
Anesthetic agents	31 (± 21)	28 (± 17)	− 3	− 10.7%	> 0.999
	34 (± 22)	30 (± 18)	− 4		
Histopathological exam	75 (± 63)	74 (± 67)	− 1	− 1.3%	0.980
	81 (± 68)	80 (± 72)	− 1		
Total intraoperative costs	2585 (± 496)	3810 (± 489)	+ 1225	+ 32.1%	< 0.001
	2807 (± 538)	4137 (± 531)	+ 1330		
Bed stay	7750 (± 6172)	6258 (± 7540)	− 1492	− 23.8%	0.340
	8416 (± 6702)	6796 (± 8187)	− 1620		
Lab test/investigations (endoscopic/radiological)	782 (± 750)	669 (± 843)	− 113	− 16.9%	0.490
	849 (± 814)	726 (± 915)	− 123		
Therapies	1020 (± 1231)	582 (± 1275)	− 438	− 75.2%	0.035
	1108 (± 1336)	632 (± 1384)	− 476		
Medical agents	434 (± 404)	415 (± 360)	− 19	− 4.6%	0.034
	471 (± 438)	451 (± 390)	− 20		
Blood products	379 (± 408)	60 (± 69)	− 319	− 531.1%	< 0.001
	412 (± 443)	65 (± 74)	− 347		
Operative procedures (endoscopic/radiological)	225 (± 670)	107 (± 400)	− 100	− 93.4%	0.315
	241 (± 727)	116 (± 368)	− 109		
Total postoperative costs	9552 (± 7890)	7509 (± 9078)	− 2043	− 27.2%	0.030
	10,373 (± 8567)	8154 (± 9857)	− 2219		
Total hospital costs	12,137 (± 7835)	11,319 (± 9150)	− 818	− 7.2%	0.807
	13,180 (± 9144)	12,291 (± 9935)	− 889		

*Values are expressed as mean ± standard deviation (SD)

Unit measure: Euro, USD

both RBC and FFP transfusions ($p < 0.001$ and p 0.001) and radio-guided/endoscopic procedures (p 0.027).

Costs

The intraoperative costs seen for completed LMH were higher than OMH (+ 31.3%, $p < 0.001$) and the main responsible resulted the expenses related to surgical devices (Table 5). On the other hand, a 71.3% reduction in postoperative costs was seen for LMH when compared to OMH (p 0.003) with all determinants of the postoperative charges showing a significant reduction. The balance between intra- and postoperative expenses resulted in a cost advantage of completed LMH with respect to their open counterpart (− 29.9%, p 0.020).

Analysis of Costs of Conversion

The average intraoperative cost of conversion resulted 517 ± 239 Euros (561 ± 259 USD), and divided as follows: theater usage and dedicated equipe 187 Euros ± 23 (203 ± 24 USD); reusable devices 196 Euros ± 16 (212 ± 17 USD); disposable devices 131 Euros ± 87 (142 ± 94 USD); anesthetic agents 3 Euros ± 1 (3 ± 1 USD).

The average postoperative cost of conversion resulted 4319 Euros ± 1178 (4690 ± 1279 USD), and divided as follows: costs of bed stay 6842 Euros ± 5421 (7429 ± 5886 USD); costs of laboratory test and investigations (endoscopic/radiological) 618 Euros ± 584 (671 ± 634 USD); costs of therapies 834 Euros ± 1030 (905 ± 1118 USD).

The average global cost of conversion resulted 4836 Euros ± 1562 (5251 ± 1696 USD).

Table 4 Comparison of perioperative outcomes, investigations and treatments between LMH and OMH groups within a per-protocol analysis

	OMH $n = 61$	LMH $n = 124$	p value*
Intraoperative outcomes			
Operative time (min)	275 (215–325)	305 (240–360)	0.047
Blood loss (mL)	950 (550–1300)	325 (200–470)	< 0.001
Red blood cells transfusion, *n* (%)	23 (37.7)	8 (6.4)	< 0.001
Fresh frozen plasma transfusion, *n* (%)	16 (26.2)	–	0.001
R0 resection, *n* (%)	55 (90.2)	111 (89.5)	> 0.999
Postoperative outcomes			
Morbidity, *n* (%)	19 (31.1)	22 (17.7)	0.003
Severity of morbidity, *n* (%)			
Mild	2 (3.3)	3 (2.4)	0.150
Moderate	13 (21.3)	15 (12.1)	0.005
Severe	4 (6.5)	4 (3.2)	0.042
Liver-specific complications, *n* (%)	23 (37.7)	16 (12.9)	0.020
Liver failure	3 (4.9)	5 (4.0)	> 0.999
Ascites	11 (18.0)	6 (4.8)	0.002
Collection	5 (6.5)	2 (1.6)	0.376
Bile leak	2 (3.3)	3 (2.4)	0.641
Cholangitis	1 (1.6)	–	> 0.999
Portal vein thrombosis	1 (1.6)	–	> 0.999
General complications, *n* (%)	19 (31.1)	18 (14.5)	0.015
Hemorrhage	1 (1.6)	–	> 0.999
Ileus	1 (1.6)	4 (3.2)	0.448
Chest infection	5 (6.5)	4 (3.2)	0.158
Cardiovascular	5 (6.5)	4 (3.2)	0.158
Urinary	2 (3.3)	3 (2.4)	> 0.999
Pancreatitis	1 (1.6)	3 (2.4)	0.530
GI bleeding	3 (4.9)	–	> 0.999
Other	1 (1.6)	–	> 0.999
Infectious complications, *n* (%)	13 (21.3)	9 (7.2)	0.013
Death, *n* (%)	1 (1.6)	–	0.250
Reoperation, *n* (%)	2 (3.3)	2 (1.6)	0.492
Readmission, *n* (%)	8 (13.1)	2 (1.6)	0.031
Total stay (days)	7 (6–7)	5 (4–9)	0.003
Radiological imaging, *n* (%)	31 (50.8)	12 (9.7)	0.003
Antibiotic therapy, *n* (%)	34 (55.7)	35 (28.2)	0.038
Albumin, *n* (%)	10 (16.4)	13 (10.5)	0.015
Diuretics, *n* (%)	39 (63.9)	23 (18.5)	< 0.001
Red blood cells transfusion, *n* (%)	34 (55.7)	12 (9.7)	< 0.001
Fresh frozen plasma transfusion, *n* (%)	19 (31.1)	13 (10.5)	0.001
Radio-guided or endoscopic procedures, *n* (%)	14 (22.9)	11 (8.9)	0.027

*The distribution of dichotomous categorical variables is expressed by percentages (absolute frequency). For continuous variables, values are expressed as median (interquartile range)

Discussion

The main finding of this study is represented by clinical outcomes of LMH more favorable if compared to open, without the association of the minimally invasive approach to any cost disadvantage.

Compared to a group of patients receiving a planned laparotomy, the clinical outcomes of laparoscopic major liver resection were advantageous in this series. Despite longer operative times, LMH exhibited lower blood loss and reduced intraoperative transfusion rates (both red blood cells and fresh frozen plasma) than OMH, in association with a comparable

Table 5 Comparison of intra-, postoperative, and total costs between LMH and OMH groups within a per-protocol analysis

	OMH $n = 61$	LMH $n = 124$	Absolute difference	% difference	p value*
Theater usage and dedicated equipe	1371 (± 380) 1489 (± 412)	1399 (± 280) 1519 (± 304)	+ 28 + 30	+ 2.0%	0.376
Reusable devices	288 (± 41) 313 (± 44)	385 (± 20) 418 (± 21)	+ 97 + 105	+ 25.2%	< 0.001
Disposable devices	820 (± 313) 890 (± 339)	1846 (± 234) 2005 (± 254)	+ 1026 + 1115	+ 55.6%	< 0.001
Anesthetic medical agents	31 (± 21) 34 (± 22)	29 (± 23) 31 (± 24)	− 2 − 3	− 6.9%	1.000
Histopathological exam	75 (± 63) 81 (± 68)	77 (± 72) 84 (± 78)	+ 2 + 3	+ 2.6%	1.000
Total intraoperative costs	2585 (± 496) 2807 (± 538)	3766 (± 365) 4090 (± 396)	+ 1181 + 1283	+ 31.3%	< 0.001
Bed stay	7750 (± 6172) 8416 (± 6702)	4745 (3746) 5153 (± 4067)	− 3005 − 3263	− 63.3%	0.003
Lab test/investigations (endoscopic/radiological)	782 (± 750) 849 (± 814)	487 (± 540) 529 (± 586)	− 295 − 320	− 60.5%	0.016
Therapies	1020 (± 1231) 1108 (± 1336)	512 (± 1147) 556 (± 1245)	− 508 − 552	− 99.2%	0.032
Medical agents	434 (± 404) 471 (± 438)	395 (± 334) 429 (± 362)	− 39 − 42	− 9.9%	0.045
Blood products	379 (± 408) 412 (± 443)	28 (± 12) 30 (± 13)	− 351 − 381	− 1253.6%	< 0.001
Operative procedures (endoscopic/radiological)	225 (± 670) 241 (± 727)	89 (± 495) 97 (± 537)	− 118 − 128	− 113.4%	0.031
Total postoperative costs	9552 (± 7890) 10,373 (± 8567)	5577 (± 5210) 6056 (± 5657)	− 3975 − 4316	− 71.3%	0.003
Total hospital costs	12,137 (± 7835) 13,180 (± 9144)	9343 (± 5260) 10,146 (± 5711)	− 2794 − 3034	− 29.9%	0.020

*Values are expressed as mean ± standard deviation (SD)

Unit measure: Euro, USD

rate of radical resections. More importantly, a significant reduction of morbidity (in particular that of moderate severity) was seen for LMH, including both general and liver-specific complications, which resulted in a lower need for postoperative radiological imaging and red blood cells transfusion rates. Noteworthy, the reduction of infectious complications and ascitic decompensation resulted into a significantly lower need for antibiotics and diuretics if compared to OMH. As a reasonable effect, patients undergoing LMH had also a significantly shorter postoperative stay.

From the financial aspect, the abovementioned clinical benefits of LMH explain the global cost-neutrality with respect to open resections, despite the higher intraoperative expenses. Significant intraoperative costs for LMH (+ 32.1% = + 1225 Euros, $p < 0.001$) were herein expected, and linked to the expenses for theater usage, dedicated health personnel and surgical devices, as found in previous reports. In fact, a highly dedicated armamentarium of reusable and disposable equipment is routinely used in surgical practice to accomplish these challenging operations, with the related costs resulting considerable. However, the expenses related to postoperative treatments (in particular medical therapies and blood products) were lower for LMH, accounting for 27.2% savings (− 2043 Euros; p 0.030) and turning into postoperative costs reduced with respect to open. In other words, the raised intraoperative expenses of LMH were counterbalanced by the postoperative savings, finally determining a global cost of LMH not superior to open resections (− 7.2% = − 818 Euros; p 0.807).

The abovementioned results arise from an intention-to-treat analysis of data, thus considering a LMH group as inclusive of both laparoscopically completed and converted resections. It is established expert's opinion that conversion to open should be pursued whenever the safety, feasibility, or oncological radicality are jeopardized, and not regarded to as the surgeon's failure. However, it has been recently demonstrated that patients undergoing laparoscopic liver resections and requiring conversion have longer operations, higher blood loss, longer hospital stay, increased frequency and severity of complications and a higher mortality rate with respect to laparoscopiccompeted resections.[22] Specifically, for LMH it has been also documented that converted patients undergo a postoperative course that is different from laparoscopically completed cases, and more similar to patients receiving planned open major hepatectomies.[23] Thus, this effect of conversion should be taken into consideration when seeking for a fair and objective assessment of the clinical and financial profile of these new procedures in comparison to the acknowledged standard. As such, the conclusions resulting from the ITT-A reflect at best the real clinical setting where a variable proportion of patients (0–40% of cases in series dedicated to LMH) inevitably requires a conversion to laparotomy to complete the procedure.

Considering the acknowledged impact of conversion on clinical outcomes, it was also hypothesized that its occurrence might have an effect from the financial point of view. Given the limited number of converted patients in this single-center series, it was not possible to evaluate the economic impact of conversion through a direct comparison of a stand-alone group of converted LMH with laparoscopic-completed and open major hepatectomies. However, the analysis undertaken following the per-protocol design allowed information on the difference in the full potential treatment effect of the newer laparoscopic and standard open techniques, and—more importantly—the calculation of the specific average cost of conversion. With this additional analysis, it was possible to compute the outcomes of a pure group of completed LMH, which appeared of great magnitude from both the clinical and economical aspect if compared to open d'emblée resection. Indeed, the clinical differences with OMH noted at the ITT-A resulted exacerbated, and a number of additional items resulted significantly more favorable for LMH (readmission rates, major morbidity, albumin and fresh frozen plasma administration, interventional radiologic, or endoscopic procedures). In parallel, the still greater intraoperative costs of LMH (+ 31.3% = + 1181 Euros; $p < 0.001$) were completely offset by the significantly lower postoperative expenses (− 71.3% = − 3975; p 0.003) and resulting in a potential 29.9% of savings in global costs if compared to the open technique (− 2794 Euros; p 0.020). However, the average cost of conversion were estimated for 4836 Euros, and mainly related to postoperative expenses (4319 Euros). This value is not negligible and provides a concrete idea of the reason why the potential cost advantage of the minimally invasive approach is mitigated by the cost of conversion, thus resulting in real total cost not different to open.

Despite having clarified that conversion to open retains specific costs, taken together the findings disclosed by this study support the value of a liver surgery program that considers the allocation of major hepatectomies by default to the laparoscopic approach, provided the context of a referral center with a high volume of minimally invasive activity is assured. In fact, despite the lack of an economic advantage, the laparoscopic approach remains globally associated with more favorable clinical results than an open approach d'emblée, as shown by the ITT-A. In our experience, the gradual development of expertise enabled a progressive reduction of the contraindications, and a parallel expansion of the candidates to the laparoscopic approach. In the present series, the significant proportion of oncologically and technically challenging cases among the LMH group (including large lesions, cirrhotic livers, patients with history of significant abdominal or hepatobiliary surgery, or requiring associated procedures such as hilar lymphadenectomy) was witnessed by an equal distribution of these difficulty factors between the laparoscopic and open group. If compared to our previously published initial experience, this progressive expansion of the pool of patients elected to a laparoscopic approach reasonably contributed—and explains—the parallel increase in our conversion rate (now 14.5 vs. 8.2%; 38.1% of which motivated by oncological safety), in any case without detrimental effect on morbidity (23.4 vs. 22.4%) and mortality rates (0.7 vs. 0%).[10]

Compared to the existing literature, this study provides further knowledge of the clinical and cost implications of LMH. Our findings support the results disclosed by a couple of well-conducted studies which documented already the cost-neutrality of LMH, however in different regional settings (UK and USA).[32,33] Despite negligible differences in the total expenses due to the variability in local currencies, this study confirms that LMH can be implemented in different healthcare systems worldwide without cost disadvantages. We herein considered both left- and right-sided major hepatectomies with a pure laparoscopic technique (while the previous reports focused on right hepatectomies). As such, this study is expected to integrate the available evidence considering that it is unlikely that surgeons willing to undertake laparoscopic major hepatectomies are starting with performing right hepatectomies before left hemihepatectomies. Finally, the conclusions that have been derived from the PP-A complete those of the intention-to-treat, and clarify the mechanism underlying the effective cost-neutrality of these procedures through a specific estimation of the costs associated with conversion.

Among the limitations, we have to acknowledge that this study took into consideration the direct hospital costs and did not evaluate the indirect costs (loss of productivity, return to work, and caregiver expenses) since those were impossible to be gathered within its retrospective design. It is believed that an analysis restricted to the direct costs may underrate the full cost effectiveness of LMH, presuming that a shorter hospitalization reasonably translates into a smooth and unimpeded convalescence. As such, studies with a prospective data collection including also the out-of-hospital costs are advocated to evaluate the cost effectiveness of these procedures, as those would reasonably consider a broader range of financial determinants. Moreover, despite an inflation-adjusted analysis is generally considered the finest method for the calculation of real prices, we took into consideration a time-span with minimal variations of the inflation in our country. As such, the estimation of the average costs herein reported can be considered a realistic picture of the financial impact of both techniques. Concerning the study design, this is a retrospective analysis where part of the pool of patients elected to major hepatectomy was allocated to the laparoscopic or open approach according to the surgeon's judgment of predetermined criteria. However, the possible influence of the selection bias on the results is likely to be reduced since part of the patients received a laparoscopic or open resection according to the enrolment in the Orange 2 Plus randomized controlled trial. Finally, it was not possible to evaluate the economic effect of conversion through a separate analysis of a stand-alone group of converted LMH, given the limited number in this single-center series. We believe this would be the interesting target of a larger and multicenter collection of data.

Conclusions

Conversions are unavoidable in a variable proportion of patients, retain specific and not negligible financial costs, and mitigate the full potential effect of the minimally invasive approach with respect to the open technique. However, despite the inherent limitations, this study supports the favorable clinical efficacy of LMH in the real setting, without being associated with any cost disadvantage. The more beneficial postoperative course associated with the minimally invasive approach is at the base of postoperative costs lower than the open counterparts, being those able to counterbalance the higher intraoperative expenses. In view of these results, it is sensible to suggest that the implementation of surgical programs of laparoscopic liver surgery including major liver resections should be incentivized by health care systems, at least in high-volume centers.

Authors' Contribution Federica Cipriani has given substantial contribution to the conception and design of the work, analysis, and interpretation of data; substantial contribution to drafting the manuscript; final approval to the version to be published; agreement to be 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.

Francesca Ratti has given substantial contribution to the acquisition, analysis, and interpretation of data; substantial contribution to drafting the manuscript; final approval to the version to be published; agreement to be 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.

Arianna Cardella has given substantial contribution to the acquisition, analysis and interpretation of data; substantial contribution to drafting the manuscript; final approval to the version to be published; agreement to be 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.

Marco Catena has given substantial contribution to the acquisition, analysis, and interpretation of data; substantial contribution to revise the manuscript critically for important intellectual content; final approval to the version to be published; agreement to be 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.

Michele Paganelli has given substantial contribution to the acquisition, analysis and interpretation of data; substantial contribution to revise the manuscript critically for important intellectual content; final approval to the version to be published; agreement to be 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.

Luca Aldrighetti has given substantial contribution to the conception and design of the work and interpretation of data; substantial contribution to revise the manuscript critically for important intellectual content; final approval to the version to be published; agreement to be 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.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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