Original article

Intrahepatic cholangiocarcinoma as the new field of implementation of laparoscopic liver resection programs. A comparative propensity score based analysis of open and laparoscopic liver resections.

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Abstract

Background

Aim of the present study is to analyze the outcomes of laparoscopic and open liver resections for (Intrahepatic CholangioCarcinoma) ICC in the modern era of laparoscopic liver surgery.

Methods

Patients undergoing laparoscopic and open liver resections for ICC in two European referral centers were included. Finally, 104 patients from the open group and 104 patients from the laparoscopic group were compared after propensity scores matching according to seven covariates representative of patients and disease characteristics. Indications to surgery, short- and long- terms outcomes were compared.

Results

Operative time, number of retrieved nodes, rate and depth of negative resection margins were comparable between the two groups. Blood loss was lower in the MILS (150 ± 100 mL, mean ± SD) compared with the Open group (350 ± 250 mL, p=0.030). Postoperative complications occurred in 14.4% of patients in the MILS and in the 24% of patients in the Open group (p=0.02). There were no significant differences in long term outcomes between groups.

Conclusions

Our results confirm feasibility, safety and oncological efficiency of the laparoscopic approach in the management of ICC. However, this surgery is often complex and should be only considered in centers with large experience in laparoscopic liver surgery.

Key Words: Laparoscopy; minimally invasive; intrahepatic cholangiocarcinoma; new technique; liver resection.

Introduction

Laparoscopic Liver Resections (LLR) is now considered routine practice in many liver centers. This exponential expansion of LLR programs was certainly supported by the documented benefits of the laparoscopic approach in terms of reduced intraoperative blood loss, postoperative morbidity and length of stay (1-4). These advantages have been achieved, without compromising oncological outcomes of patients undergoing surgery for malignant disease (1,2,5-7). Moreover, these positive outcomes are further enhanced when dealing with the most frequent form of primary liver tumors (i.e. hepatocellular carcinoma) where the level of evidence to support a strong commitment toward minimally invasiveness is high (1,2,4,5,8).

The recent Southampton Guidelines consensus on laparoscopic liver surgery (9), has strongly supported the development of the laparoscopic approach in the management of HCC, benign and metastatic disease. However, the role of the laparoscopic approach in the management of ICC was not assessed. This is possibly due to the lack of data on this specific topic and the perceived added technical difficulty when dealing with ICC.

Intrahepatic cholangiocarcinoma (ICC) represents almost 40% of primary liver tumors. Surgery, when possible, is the only potentially curative treatment for ICC (10-13) and robust data on the feasibility, safety and oncological efficiency of the laparoscopic approach in this setting is urgently needed.

In our preliminary experience on 20 patients (14), the advantages of LLR in terms of shorter hospital stay, less intraoperative blood loss and lower rate of postoperative complications were confirmed. In another small experience (14 patients) (15), oncologic outcomes were similar to those of open surgery, with the 3- and 5-year overall and disease-free survival rates comparable between LLR and open resection.

The aim of this bi-institutional propensity scores analysis is to discuss current role and limits of the application of laparoscopic approach in the management of ICC and to compare its short- and long-term outcome with the open counterpart.

Methods

Study design

Data from prospectively collected bi-institutional databases (Hepatobiliary Surgery Division, San Raffaele Hospital, Milano and University Surgical Unit, Southampton General Hospital, Southampton) was retrospectively analysed for the purpose of this study. Patients with Klatskin tumors or periductal infiltrating and intraductal cholangiocarcinomas, gallbladder cancers, unconfirmed ICC on final pathology report and less than 6 months of follow up were excluded. Outcomes of 114 patients undergoing LLR between 2009 and 2017 for mass forming ICC were compared to those of 209 patients undergoing open resection between 2004 and 2017.

The study design is shown in Figure 1a.

Approval to perform this study was obtained from the internal review board of the institution (I Go MILS protocol) and consents from subjects were waived.

Surgical technique

Open approach – Under general anaesthesia, xipho-supraumbilical incision extending to the right subcostal area was performed in subjects undergoing laparotomy.

Laparoscopic approach – A very similar surgical approach was adopted in both centers except for the patient position; in Milan, under general anesthesia, using French position with the first surgeon standing between patient's legs and having the first and the second assistant respectively on the left and on the right side of the patient, five ports were placed in a standardized configuration (16,17). In Southampton patients were operated in supine position with the surgeon moving to right and left of the patient as described on previous publications (18,19).

Intraoperative ultrasound was routinely performed to assess the liver anatomy and to confirm the resectability and relationship between the lesion and main hepatic structures. Liver transection was performed by an alternating use of the ultrasound dissector CUSA and bipolar forceps, exposing vascular structures which were selectively coagulated or sealed through clips or staplers, according to dimension. Formal lymphadenectomy was performed encompassing the complete removal of lymph node station 8 (on the common hepatic artery) and 12 (encompassing regional nodes 12a along the hepatic artery, 12b along the bile duct and 12p behind the portal vein) (16,20). Main reasons for not performing a lymphadenectomy were: time period (before lymphadenectomy entered current clinical practice in the laparoscopic series), presence of cirrhosis, diagnosis of ICC occurring only at pathological examination.

The surgical specimen was placed in an impermeable retrieval bag and taken out, without fragmentation, through a Pfannenstiel incision. Pringle's maneuver was used as required to control intraoperative bleeding.

Staging, treatment strategy and histopathological examination

Before surgery, all patients were evaluated by thoracoabdominal imaging (computed tomography and magnetic resonance imaging) and blood tests including serum concentrations of tumor markers (carcinoembryonic antigen, Ca 19.9). Selected patients also underwent positron emission tomography (PET), to rule out the presence of extrahepatic disease. Treatment strategies were systematically evaluated at weekly multidisciplinary meetings, where liver surgeons, radiologists, hepatologists and medical oncologists defined the indications for surgical procedures and both the type and the resection technique.

Histological staging was performed according to the TNM classification following the criteria of the seventh Edition of the American Joint Committee on Cancer (AJCC) (21). R0 resection was defined as the absence of tumor cells on resection margins.

Assessed variables

Data on preoperative patient and disease characteristics were collected, as well as on intraoperative and histopathological findings.

90 days morbidity was reviewed and assessed and complications were classified according to the Dindo−Clavien classification (22). Mortality was defined as any death during postoperative hospitalization or within 90 days after resection. Length of stay and time for functional recovery (defined as time to obtain the followings: adequate oral feeding, adequate pain control with oral analgesics, normal deambulation and self-care autonomy, no complications) were recorded and analyzed.

Data regarding follow up, survival status and occurrence and type of recurrence were recorded. Three- and five-year overall survival (OS) and disease-free survival (DFS) were evaluated using the Kaplan−Meier method.

Statistical methods

To minimize the effect of bias and to ensure the highest possible level of evidence in the context of a retrospective study, a 1:1 propensity score matching was performed, taking into consideration all covariates which might affect the selection and indication to the LLR or open approach or the oncological outcomes. Those covariates include age, ASA (American Society of Anesthesiology) score, presence of chronic liver disease, Ca 19.9 serum level, tumor dimension, number of tumors and tumor stage. After matching, all variables were compared using the χ^2 or Fisher's exact test for categorical data, the Mann–Whitney U test for non-normally distributed continuous data, and Student's *t*-test for normally distributed continuous variables. All data are expressed as mean plus or minus the standard deviation or median and range. Survival curves were generated and compared using the Kaplan−Meier method. Significance was defined as $p<0.05$. All analyses were performed using the statistical package SPSS 18.0 (SPSS, Chicago, IL, USA).

Results

Patients and time course of MILS and open series

Figure 1b reports the time course of MILS and open series. The ratio MILS/total resections for ICC has raised above 50% since 2014, together with a concurrent decrease in the Open/total resection ratio.

Descriptive data – before matching

Patients and disease characteristics before propensity score matching are reported in **Table 1**. Patients did not differ between the groups in age, sex, biometrics and comorbidities. Underlying liver impairment or cirrhosis secondary to viral infection and/or alcohol related damage was present in 29.8% of patients in the MILS and 24.7% in the Open group (p=0.05). Thirty-three patients in the MILS group had previous abdominal surgery (either open or laparoscopic) in their medical history. Most of patients in both groups (71.9% in the MILS and 69.9% in the Open group) had a single liver lesion. Lesion diameter was significantly larger in the MILS compared with the Open series (respectively 3.9 ± 1.3 cm versus 6.3 ± 1.2 cm, p=0.04). Eighty percent of patients in each group had a single lesion. Final pathological examination demonstrated nodal metastases in 33 of 89 (37%) patients in the MILS group and 67 of the 188 (36%) patients who had undergone lymphadenectomy in the Open group. Chemotherapy with neoadjuvant intent was administrated in a larger proportion of patients in the open compared with the laparoscopic series (6.7% versus 3.5%). Furthermore, a suspected infiltration of major vascular branches or biliary tree, requiring respectively vascular or biliary reconstructions, was more frequently detected in the open compared with the laparoscopic group.

Descriptive data – after matching

Patients and disease characteristics after propensity score matching are reported in Table 2. The quality of matching conferred comparable groups in terms of patients and disease characteristics. 88.5% of patients in the Open and 83.7% in the MILS group underwent intraoperative nodal dissection.

Short-term outcome data

Operative characteristics are shown in **Table 3**. Major hepatectomies were performed in 35 (in detail: 17 right, 17 left and 1 central hepatectomies) and 38 patients (in detail: 19 right, 17 left and 2 central hepatectomies) in the MILS and Open groups, respectively (p=NS) (18).

Length of surgery was comparable between the two groups. Laparoscopic procedures were successfully completed in 92 patients, whereas the procedure was converted to laparotomy in 12 patients. Most frequent causes of conversion were: risk of oncologic inadequacy (6 cases), bleeding (4 cases) and adhesions (2 cases). In spite of comparable intraoperative use of the Pringle maneuver in the MILS and Open group (88.5% vs 90.4%, p=ns), there was less intraoperative blood loss (150 ± 100 mL, mean ± SD) in the MILS than the Open group (350 ± 250 mL, p=0.030).

The median number of retrieved nodes, achievement of negative resection margins, and depth of surgical margins on liver parenchyma were comparable between the two groups.

Postoperative morbidity and mortality are reported in **Table 4**. Postoperative complications occurred in the 14.4% of patients in the MILS and in the 24% of patients in the Open group (p=0.02). Both the incidence of minor (Dindo-Clavien <3) and major (Dindo-Clavien ≥ 3) was reduced in the MILS group (10.6% vs 16.3%, p=0.03 and 3.9% vs 7.7%, p=0.03 respectively). The benefit in terms of reduced incidence of complications was significant when considering singularly wound infection, postoperative ileus, biliary fistula, ascites, pleural effusion and lymphatic fistula.

Both median hospital stay and time for functional recovery were reduced in the MILS (4 and 3 days respectively) compared with the Open group (6 and 4 days respectively), as well as interval time between surgery and subsequent adjuvant treatments (35 and 41 days in median, in the MILS and in the Open group respectively; p=0.04).

Long-term outcome data

Long-term outcomes are shown in **Table 5**: the results are based on a significantly different follow up available for the MILS group compared with the open group. The survival curves (Figure 2) show similar overall and disease free survival in the two groups. Overall disease recurrence rate was lower in the MILS compared with the Open group (45.2% versus 56.7%) while the recurrence pattern was similar. Recurrence at the site of the resection margin, peritoneal dissemination, or port-site metastases were not observed in any patients. Treatment of recurrences was similar between groups.

Discussion

The exponential expansion of LLR programs was certainly supported by the documented benefits of the laparoscopic approach in terms of intra- and postoperative outcome of patients, without jeopardizing oncological efficacy and long-term outcome (1-8,23-26). Whilst a high level of evidence to support minimally invasiveness is high both in the setting of hepatocellular carcinoma (2,4,5,9) and colorectal liver metastases (2,3,7-9,23-27) has been achieved, robust evidence in the contest of ICC is still lacking; this is possibly due to the particular oncological features of ICCs which have historically limited the considering of patients with this disease for a laparoscopic resection to pioneering centers. In fact, the frequent presence of large masses requiring major resections or vascular or biliary reconstructions, and the potential necessity to guarantee an adequate nodal harvesting were initially considered contraindications to laparoscopy due to the profile of high technical complexity (14).

In 2011, we described two cases of pure laparoscopic en bloc left hemihepatectomy and caudate lobe resection in ICC. (28), concluding that, in selected patients treated in centers with extensive experience, the laparoscopic approach allows an early safe discharge and quick recovery, thus optimizing surgical outcome. Only between 2015 and 2016 larger series (15,29) (respectively 14 and 11 cases) have reported comparable results of the laparoscopic approach in terms of morbidity, mortality and oncological adequacy when compared to the traditional open approach.

In 2015, we reported our preliminary results comparing 20 laparoscopic cases with 60 open cases, showing a reduced blood loss (200 vs. 350 mL, p = 0.040) with less use of the Pringle maneuver when performing laparoscopic resections (14). No significant difference in perioperative morbidity, mortality or oncological outcomes rates were observed. In that study 90% if our patients had stage I or II disease (14) reflecting the very cautious policy of we adopted in that era when considering patients for laparoscopic surgery.

Interestingly, in the recent Consensus Guidelines for Laparoscopic Liver Surgery (9) no specific indications were provided regarding cholangiocarcinoma and lymphadenectomy, suggesting more data is still needed before any conclusion on the role of the laparoscopic approach in the management of this disease can be made.

The outcomes of the present study confirm the previously reported advantages of the laparoscopic approach observed when dealing with HCC (2,4,5,9) and CRLMs (2,3,7-9,23-25) a lower blood loss, faster functional recovery and lower complications is again seen when dealing with this complex liver disease. Those results were obtained after the careful implementation of a propensity score based analysis thus reducing the effect of selection bias. Feasibility of laparoscopic approach was confirmed, being conversion rate (11.5%) and causes for conversion similar to those of laparoscopic procedures performed for other liver malignancies (2-4,5,7-9, 23-27).

Furthermore, the series provides insights into the expansion, implementation and development of the laparoscopic approach: the application of LLS in the setting of ICC was later compared with its widespread use for other indications (hepatocellular carcinoma above all). Only when the feasibility and benefits of major laparoscopic resections were reported (23,30-32) and once the limit of laparoscopic lymphadenectomy was overcome, the time course evolution of laparoscopic and open cases of ICC showed an inversion in its trend. In fact, after a steady period between 2009 and 2014 (Figure 1b), the ratio MILS/total resections for ICC raised over 50%, together with a concurrent decrease in the Open/total resection ratio. This reflects how the completion of learning curves and the development of skills and experience, in high volume centers leads to a dramatic increase of the number of patients considered for the laparoscopic approach.

Despite the clear advantages of the laparoscopic approach in ICC, some features such as possible tumor infiltration of biliary vascular structures requiring complex continue to represent a clear challenge to the laparoscopic approach and call for careful patient selection and a judicious approach to widening the surgical indication. Only few case reports or small series of biliary reconstructions are available in the literature (33,34), since the use of laparoscopy has not gained popularity in hilum infiltrating tumors. Overall, the open series in the present study still includes patients with more advanced disease, as indicated by higher levels of Ca 19.9 and larger tumor size in this group. On the contrary, a strong motivation towards minimally invasiveness is perceived when liver parenchyma is impaired: most data from the literature suggest, with high level of evidence, that laparoscopic approach is the only independent factor to reduce the complication rate, and especially the incidence of postoperative ascites, liver failure and morbidity assessed in terms of ''Comprehensive Complication Index"(9).

After MILS and open series were matched using propensity scores, the comparison between the MILS and the Open groups resulted in a lower morbidity (14.4% in the MILS and 24% in the Open group, p=0.02) and reduced blood loss (150 ± 100 mL versus 350 ± 250 mL respectively, p=0.03). Furthermore, MILS group experienced shorter length of stay and faster functional recovery thanks to reduced surgical stress: this benefit is the result of both the lower biological impact of laparoscopy (35) and the strong adoption of fast track management protocols that were initially introduced in the context of minimally invasive surgery (36-39).

Long term advantages in the MILS group should be interpreted with caution due to a still short period of follow up of most patients. Despite this it is interesting to underline that the shorter time for functional recovery and return to social life has allowed an earlier start of adjuvant treatments (35 and 41 days in median, in the MILS and in the Open group respectively; p=0.04). The hypothesis that the favorable biological effect of laparoscopy (35) has a positive impact on long term outcomes, especially reducing the risk of recurrence due to a reduced impairment of natural immune response, is still far from being demonstrated but is for sure an interesting field for future focused studies.

Our study was not specifically designed to address the indication and impact of laparoscopic lymphadenectomy in the management of ICC, however, it is important to underline that this was performed in a higher proportion of patients in the Open group (88.5% versus 83.7%).

This could be explained by different time period time, (before lymphadenectomy entered current clinical practice in the laparoscopic series) and presence of cirrhosis which could be a risk factor for lymphadenectomy related complications.

Currently, many authors would disagree with the routine need of hilar lymphadenectomy, suggesting that its role may only be for occasional staging purposes; on the other hands, many others sustain its curative role and recommend it (20). To date, the role of upfront lymphadenectomy in the treatment of ICC is still controversial and despite the incidence of nodal involvement is almost 40% in surgical series and N1 is recognized as a negative prognostic factor indeed (40-42), recent data show that only 55% of resected patients are submitted to pathologic evaluation of at least one regional node (41,42). It is presumable that, together with the technical evolution of laparoscopic technique within the learning curve, a progressively higher proportion of patients undergoing MILS resection for ICC will undergo lymphadenectomy.

The evaluation of adequacy of laparoscopic approach to address the need of a formal lymphadenectomy in biliary tumors, as well as long-term oncologic evaluation, was specifically analysed in a study by our group comparing results from minimally invasive and open lymphadenectomy (43). Results allowed to conclude that technical proficiency of laparoscopic liver resection permit to extend the adoption of minimally invasive techniques, being nodal dissection adequate in terms of number of harvested nodes, without increased risks of lymphadenectomy-related morbidity (43).

In this setting it would be interesting to analyze the effect of laparoscopy on the incidence and the risk of lymphadenectomy related complications which presently constitute a disincentive in the treatment of ICC arising in the context of cirrhosis. Indeed a recent report by Bagante et al. (40) described an increased risk of postoperative complications in patients undergoing lymphadenectomy who had concomitant cirrhosis which is a relatively common situation in patients developing cholangiocellular neoplasms (1 in 10 patients).

The present series includes only cases of mass-forming intrahepatic cholangiocarcinoma, without taking into account small lesions originating close to the hepatic hilum and behaving like perihilar forms. Despite perihilar and intrahepatic forms indeed may have some common features and consequently be associated with common challenges, they should be addressed separately. Anyway, large mass-forming intrahepatic cholangiocarcinomas, while disrupting the normal anatomy of liver parenchyma, may even infiltrate hilar structures, as preoperatively suspected in some cases (4 in the MILS Group and 6 in the Open Group, after PSM) of the present series. Lesion dimension as well as suspected infiltration of vascular or biliary structures are not considered an absolute contraindication for laparoscopic approach, although they may hinder minimally-invasive feasibility and be associated with a higher risk of conversion to open approach. Recently however, the possibility to perform biliary confluence resection for perihilar forms has been reported, with favorable outcomes. Consequently, we assume that the same feasibility can be reproduced even in intrahepatic forms, although the analysis of laparoscopic biliary resections was beyond the aims of the present study (44).

A weakness of our study may be the retrospective nature and the institutional variation in surgical practice (45). However, these results come from a large and contemporary cohort of patients, after the implementation of propensity score matching to balance most important oncological factors. Despite a bi-institutional analysis could imply differences in technical details, management protocols and oncological strategies, we did not observe any significant differences in the preoperative, operative and post-operative management to the best of our knowledge, this is also the largest study on the role of the laparoscopic approach in the management of ICC documenting the feasibility and safety of this approach in the contest of this rarely discussed disease (without the possibility of alternative curative treatments other than surgery) (46).

In conclusion, in selected patients, laparoscopic liver resection for ICC is feasible and can be associated with reduced intraoperative blood loss, lower complication rate, faster functional recovery and earlier return to oncological treatments. However, this is associated with significant technical challenges (frequently requiring major hepatectomies and locoregional lymphadenectomy), hence a wide experience in laparoscopic liver surgery and a careful case assessment and selection are needed for a safe implementation.

Disclosure

The material has not been previously published or submitted elsewhere for publication and will not be sent to another journal until a decision is made concerning publication. All listed authors have participated in the study and have approved the final manuscript. Francesca Ratti, Arab Rawashdeh, Federica Cipriani, John Primrose, Guido Fiorentini, Mohammed Abu Hilal, Luca Aldrighetti have no personal conflicts of interest or financial disclosure.

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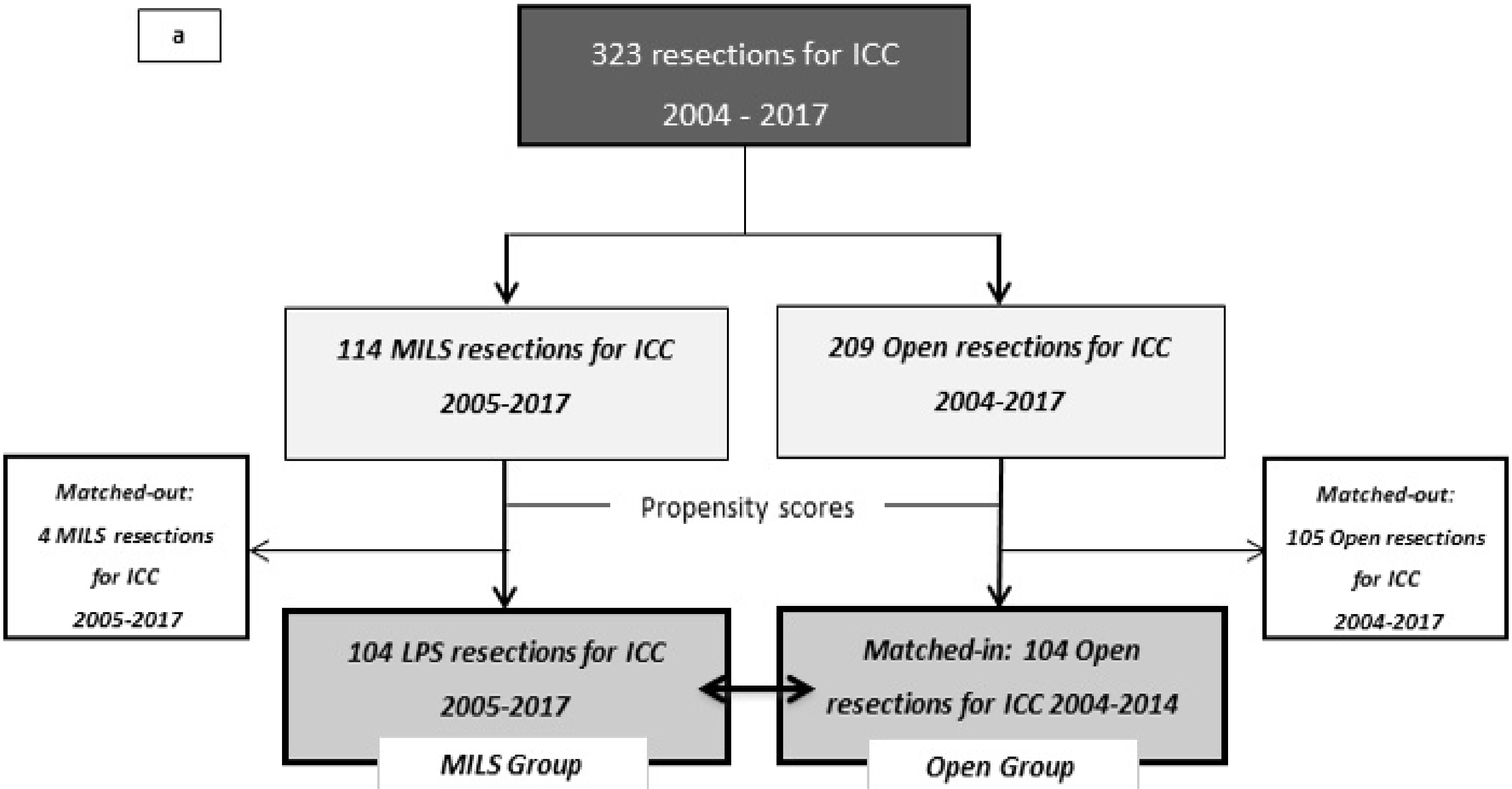
Figure captions

Figure 1. a. Study design. b. Time course of liver resections in the whole series and in the open and laparoscopic groups. The arrow indicates the moment of trend-inversion between open and laparoscopic approach.

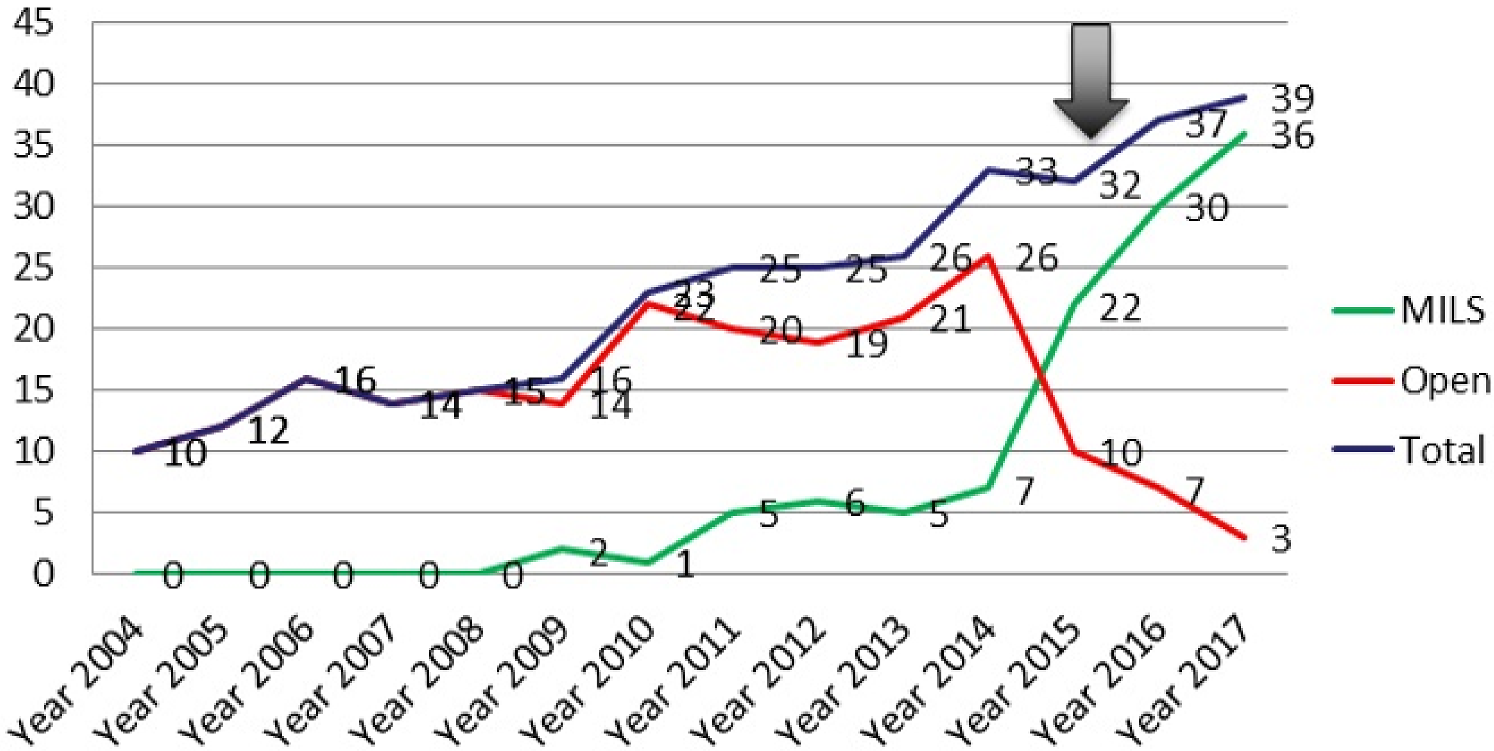
Figure 2. 2a Overall survival according to treatment group. 2b Disease free survival according to treatment group.

a



323 resections for ICC
2004 - 2017
114 MILS resections for ICC
2005-2017
209 Open resections for ICC
2004-2017
Propensity scores
Matched-out:
4 MILS resections
for ICC
2005-2017
Matched-out:
105 Open resections
for ICC
2004-2017
104 LPS resections for ICC
2005-2017
MILS Group
Matched-in: 104 Open
resections for ICC 2004-2014
Open Group

b



45
40
35
30
25
20
15
10
5
0
Year 2004
Year 2005
Year 2006
Year 2007
Year 2008
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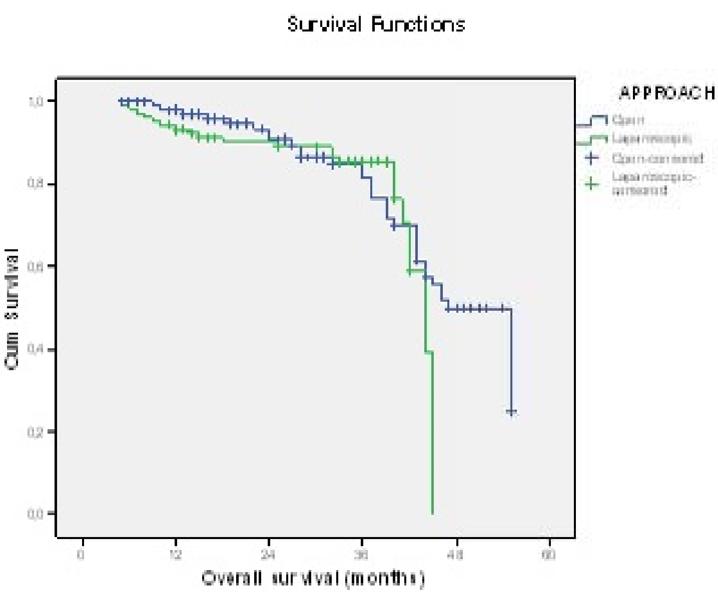
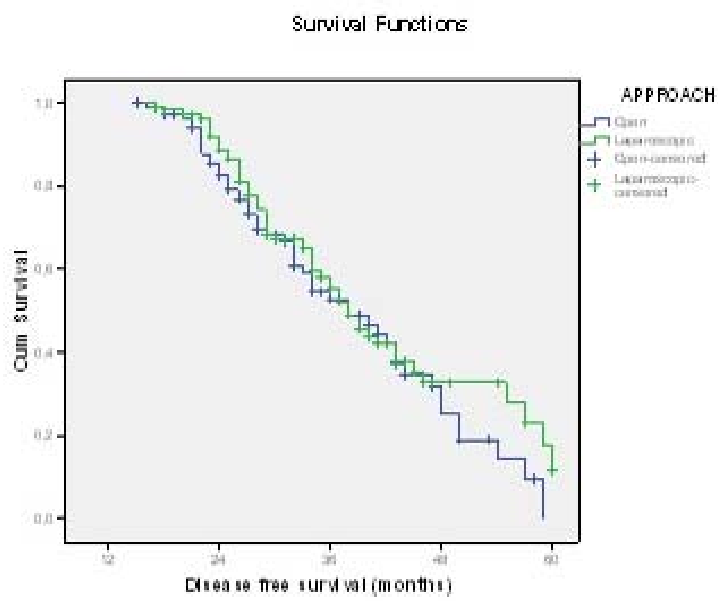
Year 2010
Year 2011
Year 2012
Year 2013
Year 2014
Year 2015
Year 2016
Year 2017
MILS
Open
Total

a


Survival Functions
Cum Survival
Overall survival (months)
APPROACH
Open
Laparoscopic
Open-censored
Laparoscopic-censored

b


Survival Functions
Cum Survival
Disease free survival (months)
APPROACH
Open
Laparoscopic
Open-censored
Laparoscopic-censored

		MILS Group (n=114)	Open Group (n=209)	p
Age (years)	*Mean ± SD*	60 ± 5	62 ± 6	ns
Male sex, n(%)		70 (61.4)	120 (57.4)	ns
ASA score, n (%)				ns
	1	25 (21.9)	43 (20.6)	
	2	60 (52.6)	116 (55.5)	
	3	29 (25.4)	50 (23.9)	
BMI	*Mean ± SD*	24.2 ± 1.8	24.8 ± 2.6	ns
Underlying liver disease, n(%)				0.05
	None	80 (70.2)	159 (76.3)	
	Steatosis/mild impairment	19 (16.7)	32 (15.3)	
	Cirrhosis	15 (13.2)	18 (8.6)	
Previous abdominal surgery, n(%)				0.05
	None	81 (71.1)	164 (78.5)	
	Yes, supramesocolic	24 (21.1)	27 (12.9)	
	Yes, inframesocolic	9 (7.9)	17 (8.1)	
CEA (ng/mL)	*Mean ± SD*	33 ± 14	45 ± 32	ns
Ca 19.9 (U/mL)	*Mean ± SD*	89 ± 76	153 ± 64	0.03
Size (cm)	*Mean ± SD*	3.9 ± 1.3	6.3 ± 1.2	0,04
Positive nodal status at imaging, n(%)		13 (11.4)	45 (21.5)	ns
Tumor number, n(%)				ns
	Single	82 (71.9)	146 (69.9)	
	Single with satellites	16 (14.0)	34 (16.3)	
	Multiple	15 (13.2)	29 (13.9)	
Histological grade, n(%)				ns
	Well	15 (13.2)	17 (8.1)	
	Moderate	81 (71.1)	170 (81.3)	
	Poor	18 (15.8)	22 (10.5)	
T stage, n(%)				ns
	T1/T2	84 (73.7)	159 (76.1)	
	T3/T4	30 (26.3)	50 (23.9)	
Lymphadenectomy, n(%)		89 (78.1)	188 (89.9)	0.04
Nodal status, n(%)				ns
	Negative	56 (62.9)	121 (64.4)	
	Positive	33 (37.1)	67 (35.6)	
Staging, n(%)*				ns
	I/II	69 (60.5)	130 (62.2)	
	III/IVa	45 (39.5)	79 (37.8)	
Preoperative CT, n(%)				0.05
	Yes	4 (3.5)	14 (6.7)	
	No	110 (96.5)	195 (93.3)	
Suspected need for vascular resection, n(%)		0 (0)	15 (7.2)	
Suspected need for biliary resection, n(%)		4 (3.5)	25 (12)	

Abbreviations: ASA, America Society of Anesthesiology; BMI, Body Mass Index; CA, Carbohydrate antigen; CEA, Carcinoembryonic antigen; T, Tumor; CT, ChemoTherapy; ns, not significant.

*** Percentage is referred to number of patients undergoing lymphadenectomy**

**** Defined according to 8th Edition of AJCC Classification**

Table 1. Patients and disease characteristics before propensity score matching.

		MILS Group (n=104)	Open Group (n=104)	p
Age (years)*	*Mean ± SD*	59 ± 5	61 ± 6	ns
Male sex, n(%)		70 (67.3)	68 (65.4)	ns
ASA score, n (%)*				ns
	1	22 (21.2)	20 (19.2)	
	2	56 (53.8)	58 (55.8)	
	3	26 (25)	26 (25.0)	
BMI	*Mean ± SD*	24.1 ± 1.9	24.6 ± 1.6	ns
Underlying liver disease, n(%)*				ns
	None	74 (71.2)	72 (69.2)	
	Steatosis/mild impairment	17 (16.3)	19 (18.3)	
	Cirrhosis	13 (12.5)	13 (12.5)	
Previous abdominal surgery, n(%)				ns
	None	81 (77.9)	81 (77.9)	
	Yes, supramesocolic	24 (23.1)	26 (25.0)	
	Yes, inframesocolic	9 (8.7)	7 (6.7)	
CEA (ng/mL)	*Mean ± SD*	23 ± 10	25 ± 12	ns
Ca 19.9 (U/mL)*	*Mean ± SD*	86 ± 79	95 ± 70	ns
Size (cm)*	*Mean ± SD*	3.9 ± 1.7	4.1 ± 1.2	ns
Positive nodal status at imaging, n(%)		13 (12.5)	16 (15.4)	ns
Tumor number, n(%)*				ns
	Single	73 (70.2)	71 (68.3)	
	Single with satellites	16 (15.4)	17 (16.3)	
	Multiple	15 (14.4)	16 (15.4)	
Histological grade, n(%)				ns
	Well	14 (13.5)	12 (11.5)	
	Moderate	73 (70.2)	83 (79.8)	
	Poor	17 (16.3)	14 (13.5)	
T stage, n(%)*				ns
	T1/T2	79 (76.0)	81 (77.9)	
	T3/T4	25 (24.0)	23 (22.1)	
Lymphadenectomy, n(%)		87 (83.7)	92 (88.5)	0.05
Nodal status, n(%)**				ns
	Negative	55 (63.2)	61 (66.3)	
	Positive	32 (36.8)	31 (33.7)	
Staging, n(%)***				ns
	I/II	74 (71.2)	75 (72.1)	
	III/IVa	40 (38.5)	39 (37.5)	
Preoperative CT, n(%)				ns
	Yes	3 (2.9)	4 (3.8)	
	No	101 (97.1)	100 (96.2)	
Suspected need for vascular resection, n(%)		0 (0)	2 (1.9)	
Suspected need for biliary resection, n(%)		4 (3.8)	6 (5.8)	

Abbreviations: ASA, America Society of Anesthesiology; BMI, Body Mass Index; CA, Carbohydrate antigen; CEA, Carcinoembryonic antigen; T, Tumor; CT, ChemoTherapy; ns, not significant.

*** Covariate used for propensity score matching**

**** Percentage is referred to number of patients undergoing lymphadenectomy**
**** Defined according to 8th Edition of AJCC Classification**

Table 2. Patients and disease characteristics after propensity score matching.

		MILS Group (n=104)	Open Group (n=104)	p
Procedure, n(%)*				ns
	Minor resection	69 (66.3)	66 (63.5)	
	Major resection	35 (33.7)	38 (36.5)	
Pringle Manuevre, n (%)				ns
	Not performed	12 (11.5)	10 (9.6)	
	Performed	92 (88.5)	94 (90.4)	
Lenght of surgery (min)	*Median (range)*	270 ± 65	230 ± 60	ns
Blood Loss (mL)	*Median (range)*	150 ± 100	350 ± 250	0.03
Number of retrieved nodes	*Median (range)*	8 (5-11)	7 (5-14)	ns
Surgical margin, n (%)				ns
	R0	101 (97.1)	99 (95.2)	
	R1	3 (2.9)	5 (4.8)	
Conversion, n(%)		12 (11.5)	n.a.	
Surgical margin (mm)	*Mean ± SD*	9 ± 4	8 ± 4	ns
Intraoperative blood transfusions, n (%)				0.04
	No	100 (96.2)	96 (92.3)	
	Yes	4 (3.8)	8 (7.7)	
Postoperative blood transfusions, n (%)				0.03
	No	97 (93.3)	89 (85.6)	
	Yes	7 (6.7)	15 (14.4)	
Functional recovery (days)	*Median (range)*	3 (1-5)	4 (3-10)	0.05
Lenght of stay (days)	*Median (range)*	4 (2-10)	6 (3-21)	0.04
Interval surgery-adjuvant treatment (days)	*Median (range)*	35 (30-45)	41 (37-59)	0.04

Abbreviations: ASA, America Society of Anesthesiology; BMI, Body Mass Index; CA, Carbohydrate antigen; CEA, Carcinoembryonic antigen; T, Tumor; CT, ChemoTherapy; ns, not significant.

*** Covariate used for propensity scores matching**

Table 3. Intra- and postoperative details

		MILS Group (n=104)	Open Group (n=104)	p
Complications, n (%)				
	Hemorrhage	0	2 (1.9)	ns
	Wound infection	1 (1.0)	4 (3.8)	0.05
	Ileus	1 (1.0)	5 (4.8)	0.01
	Biliary fistula	4 (3.8)	8 (7.7)	0.03
	Transient liver failure	3 (2.9)	5 (4.8)	ns
	Ascites	7 (6.7)	11 (10.6)	0.04
	Pleural effusion	7 (6.7)	10 (9.6)	0.05
	Pneumonia	1 (1.0)	3 (2.9)	ns
	Fever	4 (3.8)	6 (5.8)	ns
	Pancreatitis	2 (1.9)	2 (1.9)	ns
	Lymphatic fistula	2 (1.9)	7 (6.7)	0.03
	Arrythmia	3 (2.9)	4 (3.8)	ns
	DVT/PE	1 (1.0)	2 (1.9)	ns
Morbidity, n(%)		15 (14.4)	25 (24.0)	0.02
Grade of complications, n (%)*				
Minor	*I grade*	3 (2.9)	5 (4.8)	0.03
	II grade	8 (7.7)	12 (11.5)	
Major	*III grade*	3 (2.9)	6 (5.8)	0.03
	IV grade	1 (1.0)	2 (1.9)	
Mortality, n(%)		1 (1.0)	2 (1.9)	ns

Abbreviations: ns, not significant

*** Classified according to Dindo-Clavien classification of surgical complications**

Table 4. Postoperative morbidity and mortality

		MILS Group (n=104)	Open Group (n=104)	p
Follow up (months)	*Median (range)*	39 (17-62)	50 (17-60)	0.04
Death (n,%)		22 (21.2)	33 (31.7)	0.04
Cause of death (n,%)*				ns
	Tumor progression	22 (100)	32 (97.0)	
	Other	0 (0)	1 (3.0)	
Disease free survival (months)	*Median (range)*	31 (6-45)	32 (3-60)	ns
Disease recurrence (n,%)		47 (45.2)	59 (56.7)	0.05
Modality of recurrence, n(%)				ns
	Nodal	4 (8.5)	7 (11.9)	
	Intrahepatic, monofocal	17 (36.2)	22 (37.3)	
	Intrahepatic, multifocal	18 (38.3)	26 (44.1)	
	Extrahepatic	8 (17)	14 (23.7)	
Therapy of recurrence, n(%)				ns
	Re-resection	11 (23.4)	15 (25.4)	
	Medical therapy	27 (57.4)	37 (62.7)	
	Other local treatments	9 (19.1)	7 (11.9)	

*Percentage is referred to the number of patients who died

Abbreviations: ns, not significant

Table 5. Long term outcomes.