

## Perioperative and Long-Term Outcomes of Laparoscopic Versus Open Lymphadenectomy for Biliary Tumors: A Propensity-Score-Based, Case-Matched Analysis

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### ABSTRACT

**Background.** The purpose of this study was to compare patients undergoing MILS and open liver resections with associated lymphadenectomy for biliary tumors (intrahepatic cholangiocarcinoma and gallbladder cancer) in a case-matched analysis using propensity scores.

**Methods.** A total of 104 consecutive patients underwent liver resection with associated locoregional lymphadenectomy by laparoscopic approach constituted the study group (MILS group). The MILS group was matched in a ratio of 1:2 with patients who had undergone open resection for primary biliary cancers (Open group). Short- and long-term outcomes were evaluated and compared, with specific focus on specific details of lymphadenectomy.

**Results.** Laparoscopic series resulted in a statistically significant lower blood loss (200 vs. 350,  $p = 0.03$ ), minor intraoperative blood transfusions (3.2% vs. 7.9%,  $p = 0.04$ ), and postoperative blood transfusions (10.5% vs. 15.8%), other than shorter length of stay (4 vs. 6 days,  $p = 0.04$ ). Number of retrieved nodes was 8 versus 7 ( $p =$  not significant); particularly, percentage of patients who achieved the recommended AJCC cutoff of six lymph nodes harvested were 93.7% versus 85.8% ( $p = 0.05$ ). Both overall and lymphadenectomy-related morbidity (bleeding, pancreatitis, lymphatic fistula, vascular, and biliary injuries) were lower in MILS group (respectively 16.3% and 3.2% vs. 22.1% and 5.3%,  $p = 0.03$ ). Median disease-free survival was 33 versus 36 months and disease recurrence

occurred in 45.3% versus 55.3% of patients in MILS and Open groups respectively.

**Conclusions.** Laparoscopic approach for lymphadenectomy is a valid option in patients with biliary cancers, because it allows to maintain the advantages of minimally invasive approach, without compromising the accuracy and the outcomes of nodal dissection.

A formal lymphadenectomy (LND) for biliary malignancies, irrespectively of macroscopic nodal involvement, is suggested by many authors to obtain adequate staging information, being lymph node metastases one of the most important independent prognostic factors for long-term outcome.<sup>1–5</sup> In resected specimens, incidence of nodal involvement is reported between 30 and 50% and long-term outcome of patients with positive nodes is dismal, so that this finding guides decision-making regarding the need for adjuvant treatments.<sup>6–9</sup> Furthermore, a possible prognostic advantage of upfront lymphadenectomy to reduce the incidence of locoregional recurrence has been recently proposed despite a strong level of evidence to support this hypothesis is still lacking.<sup>10</sup> Disease diffusion along lymphatic vessels seems to involve as first nodes of the hepatoduodenal ligament (station 12) and of the hepatic artery (station 8), which should be removed in all of the patients.<sup>11</sup> Although the minimum number of nodes to be retrieved is presently an open issue, the eighth edition of the AJCC recommends a cutoff of six harvested nodes.<sup>12,13</sup> In this scenario, the technical challenges of laparoscopic nodal dissection have constituted a restraint for the implementation of minimally invasive techniques in tumors arising from biliary tract.

In a previous report from our group, analyzing an initial experience on ten patients with intrahepatic cholangiocarcinoma, laparoscopic lymphadenectomy was proved to be

feasible and comparable with open approach in terms of number of retrieved nodes when performed by surgeons with extensive expertise and training.<sup>14</sup> Indeed, even in the setting of biliary cancers, minimally invasive surgery should not justify an amendment of the basic rules of oncologic disease treatment.

Interestingly, despite the widespread diffusion of minimally invasive approach (MILS) for the treatment of liver lesions given its well-recognized advantages over open surgery, the incidence of biliary cancers in laparoscopic series is still poor and the topic of lymphadenectomy has never been specifically addressed, to our knowledge.

The purpose of this study was to compare patients undergoing MILS and open liver resection *with associated lymphadenectomy for biliary tumors* (intrahepatic cholangiocarcinoma and gallbladder cancer) in a case-matched analysis using propensity scores. The primary endpoint was adequacy of MILS approach (feasibility, number of retrieved nodes, and specific morbidity), and the secondary endpoints were long-term oncologic outcomes (in particular disease-free survival and locoregional recurrence).

## METHODS

### *Study Design*

Between January 2004 and October 2017, data from 2510 liver resections performed at the Hepatobiliary Surgery Division of San Raffaele Hospital, Milano were prospectively collected in a database and are now retrospectively reviewed. During the study period, 489 resections for histologically confirmed primary biliary cancer (including both intrahepatic and perihilar cholangiocarcinoma and gallbladder cancer) were performed. Of these, from 2011 on (when indications to MILS approach were extended to encompass patients requiring nodal dissection), 104 consecutive patients underwent liver resection with associated locoregional lymphadenectomy by laparoscopic approach; these constituted the study group (MILS group). The MILS group was matched in a ratio of 1:2 with patients who had undergone open resection for primary biliary cancers (Open group, constituting the control group). The matching was achieved based on scores including the following eight covariates: age, American Society of Anesthesiology (ASA) score, diagnosis, underlying liver disease, radiological nodal status, nodularity, tumor dimensions, T stage, and extent of hepatectomy. Procedures were identified after excluding procedures with any of the following characteristics: patients who did not received lymphadenectomy, re-resections, need for associated vascular or biliary

reconstruction, major vascular involvement or thrombosis, or less than 6 months of follow-up.

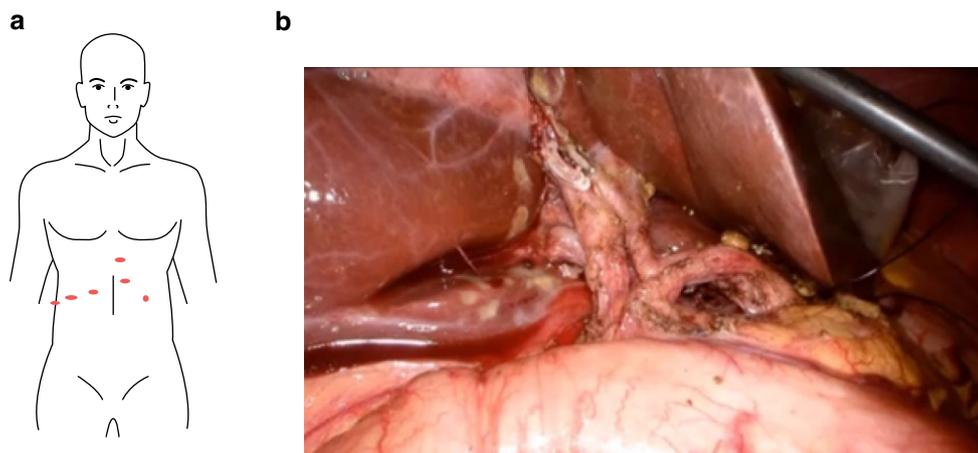
### *Participants and Procedures*

Approval to perform this retrospective study was obtained from the Institutional Review Board of our institution, and the requirement for consents from subjects was waived.

**Laparoscopic Approach** 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 (inverted J shape; Fig. 1a).<sup>15</sup>

**Open Approach** Under general anaesthesia, xiphosupraumbilical incision extending to the right subcostal area was performed in subjects undergoing laparotomy.

Intraoperative ultrasound was routinely performed to assess liver anatomy and to confirm resectability and relationship between the lesion and main hepatic structures. LND was generally performed as the first surgical step, before proceeding with the planned hepatic transection. 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). A possible extension to station 13 (lymph nodes on the posterior surface of the pancreatic head) or to station 9 (lymph nodes of the celiac trunk) was considered if the preoperative workup was consistent with macroscopic nodal involvement. Lymph nodes dissection is performed at the beginning of the procedure, before liver resection. It starts at the celiac trunk, detecting the origin of the common hepatic artery, and it is conducted up to completely skeletonizing the common hepatic artery, upon its entrance into the hepatoduodenal ligament. The use of a device both capable of sealing and cutting contemporaneously is helpful in this phase, alternatively using the hook and bipolar forceps for a particularly precise dissection. During this time of dissection, the left gastric artery should be recognized arising from the celiac trunk, avoiding to interrupt or to damage accessory arteries deriving from it and feeding the left hepatic lobe. Once obtained a complete dissection of the common hepatic artery, a complete removal of the lymphatic tissue encompassed into the hepatoduodenal ligament is required. Acute dissection is mandatory to avoid any injury to the common bile duct, to the right and left branches of the hepatic artery and to the portal trunk. Surgical field at the end of nodal dissection is



**FIG. 1 a** Trocar disposition. Hasson trocar is placed in right pararectal fossa, whereas the other four 5- to 12-mm trocars were placed in right flank (2 trocars), in epigastrium and left

hypochondrium. An additional incision is performed to house the chest tube to perform the Pringle maneuver. **b** Surgical field after nodal dissection

shown in Fig. 1b. The approach to LND for biliary tract malignancies was never modified over the years and, in particular, the indication for LND and its extent was maintained along the whole period. Liver transection is performed by an alternating use of the ultrasound dissector and bipolar forceps, exposing vascular structures which were selectively coagulated or sealed through clips or staplers, according to dimension.

#### *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). Positron emission tomography (PET) was performed to screen for extrahepatic disease. Treatment strategies were systematically evaluated at weekly multidisciplinary meetings, where liver surgeons, radiologists, and medical oncologists defined the indications for surgical procedures and both the type and the resection technique.

Tumors were staged histologically according to the TNM classification following the criteria of the eight Edition of the American Joint Committee on Cancer (AJCC).<sup>16</sup> Resections were considered curative (R0) when margins had no evidence of microscopic disease.

#### *Assessed Variables*

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

90 days were reviewed and assessed retrospectively according to the Dindo–Clavien classification.<sup>17</sup> Lymphadenectomy-related morbidity was assessed in terms of bleeding, pancreatitis, lymphatic fistula, vascular, and biliary injuries. Lymphatic fistula was defined when triglycerides level in drainage fluid was  $> 110$  mg/dL.<sup>18</sup> Mortality was defined as any death during postoperative hospitalization or within 90 days after resection.

Data regarding follow-up, survival status, and recurrence 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 adjust for the different covariate distributions of the two groups, matching control patients who had undergone open surgery were selected according to propensity scores based on seven covariates in a ratio of 1:2 with the MILS group. After matching, all variables were compared using the  $\chi^2$  or Fisher's exact test for categorical data, the Mann–Whitney  $U$  test for nonnormally 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).

## RESULTS

### Participants

Between 2004 and 2017, 489 resections for histologically confirmed primary biliary cancer were performed. Of these, 104 patients received laparoscopic lymphadenectomy for ICC from 2011 to 2017. A total of 208 open cases resulted after application of the aforementioned eight covariates, conferring a 1:2 matching ratio.

### Descriptive Data

Patients and disease characteristics are reported in Tables 1 and 2. There were no statistically significant differences in terms of age (mean 59 vs. 62 years), sex (male percentage 61.1% vs. 57.9%), comorbidities (mean BMI 23.3 vs. 23.9), underlying liver steatosis (14.7% vs. 15.3%), cirrhosis (10.5% vs. 8.4%), and previous abdominal surgery (74% vs. 78.4%), which was itself not considered a contraindication to minimally invasive approach.

Final pathology was consistent with intrahepatic cholangiocarcinoma (84 vs. 162, 81.1% vs. 77.9%) and gallbladder cancer (20 vs. 46, 18.9% vs. 22.1%): mean size in cm (3.9 vs. 4.3), number of nodules (single lesions in 80% vs. 80%, associated single satellites in 10.5% vs. 11.1%, multiple nodules 9.5% vs. 8.9%), histologic grade (G1 10.5% vs. 8.4%, G2 74.7% vs. 81.6%, G3 4.7% vs.

10%) and staging (T1/2 78.9% vs. 76.3%; T3/4 21.1% vs. 23.7%) did not differ significantly among two groups. Final pathologic examination demonstrated nodal metastases in 32.6% versus 34.7%, whereas nodal status malignancy at preoperative imaging was 12.6% versus 17.4%.

### Outcome Data

All procedures were performed by the same surgical team. Operative characteristics are shown in Table 3. Major resections were performed in 17 and 38 cases (17.9% vs. 20%), whereas minor resections were 78 and 152 (82.1% vs. 80%,  $p =$  not significant).

### Primary Endpoint: Intra- and Postoperative Outcome

Feasibility: laparoscopic resections resulted in longer procedures (240 vs. 210 min), although this was not statistically significant. Conversion rate was 10.5%, comparable with conversion rate of major abdominal laparoscopic procedures. Laparoscopic series resulted in a statistically significant lower blood loss (200 vs. 350,  $p = 0.03$ ), minor intraoperative blood transfusions (3.2% vs. 7.9%,  $p = 0.04$ ) and postoperative blood transfusions (10.5% vs. 15.8%), other than shorter length of stay (4 vs. 6 days,  $p = 0.04$ ).

Postoperative outcomes in the overall series are shown in Table 4. A lower number of patients in laparoscopic group experienced postoperative morbidity (16.3% vs.

**TABLE 1** Patient characteristics

|   | MILS group ( $n = 104$ ) | Open group ( $n = 208$ ) | $p$ |
|---|--------------------------|--------------------------|-----|
| <i>Age (years)<sup>a</sup></i>                                  |                          |                          |     |
| Mean $\pm$ SD   | 59 $\pm$ 6               | 62 $\pm$ 5               | ns  |
| Male sex, $n$ (%)   | 64 (61.1)                | 120 (57.9)               | ns  |
| <i>ASA score, <math>n</math> (%)<sup>a</sup></i>                |                          |                          | ns  |
| 1   | 22 (21.1)                | 45 (21.6)                |     |
| 2   | 56 (53.7)                | 113 (54.2)               |     |
| 3   | 26 (25.3)                | 50 (24)                  |     |
| <i>BMI</i>  |                          |                          |     |
| Mean $\pm$ SD   | 23.3 $\pm$ 1.3           | 23.9 $\pm$ 1.6           | ns  |
| <i>Underlying liver disease, <math>n</math> (%)<sup>a</sup></i> |                          | ns                       |     |
| None  | 78 (74.7)                | 159 (76.3)               |     |
| Steatosis/mild impairment                                       | 15 (14.7)                | 32 (15.3)                |     |
| Cirrhosis   | 11 (10.5)                | 17 (8.4)                 |     |
| <i>Previous abdominal surgery, <math>n</math> (%)</i>           |                          | ns                       |     |
| None  | 77 (74)                  | 163 (78.4)               |     |
| Yes, supramesocolic   | 21 (20)                  | 27 (13.2)                |     |
| Yes, inframesocolic   | 6 (5.3)                  | 17 (8.4)                 |     |

ASA America Society of Anesthesiology; BMI body mass index; ns not significant

<sup>a</sup>Covariate used for propensity scores matching

**TABLE 2** Disease characteristics

|  | MILS group (n = 104) | Open group (n = 208) | p  |
|--|----------------------|----------------------|----|
| <i>CEA (ng/mL)</i>                             |                      |                      |    |
| Mean ± SD                                      | 29 ± 11              | 20 ± 22              | ns |
| <i>Ca 19.9 (U/mL)</i>                          |                      |                      |    |
| Mean ± SD                                      | 89 ± 21              | 101 ± 34             | ns |
| <i>Size (cm)<sup>a</sup></i>                   |                      |                      |    |
| Mean ± SD                                      | 3.9 ± 1.3            | 4.3 ± 1.2            | ns |
| <i>Diagnosis, n (%)<sup>a</sup></i>            |                      |                      | ns |
| Intrahepatic cholangiocarcinoma                | 84 (81.1)            | 162 (77.9)           |    |
| Gallbladder cancer                             | 20 (18.9)            | 46 (22.1)            |    |
| <i>Positive nodal status at imaging, n (%)</i> | 13 (12.6)            | 36 (17.4)            | ns |
| <i>Tumor number, n (%)<sup>a</sup></i>         |                      |                      | ns |
| Single   | 83 (80)              | 166 (80)             |    |
| Single with satellites                         | 11 (10.5)            | 23 (11.1)            |    |
| Multiple                                       | 10 (9.5)             | 19 (8.9)             |    |
| <i>Histological grade, n (%)</i>               |                      |                      | ns |
| Well   | 11 (10.5)            | 17 (8.4)             |    |
| Moderate                                       | 78 (74.7)            | 170 (81.6)           |    |
| Poor   | 15 (14.7)            | 21 (10)              |    |
| <i>T stage, n (%)<sup>a</sup></i>              |                      |                      |    |
| T1/T2  | 82 (78.9)            | 159 (76.3)           |    |
| T3/T4  | 22 (21.1)            | 49 (23.7)            |    |
| <i>Nodal status, n (%)<sup>b</sup></i>         |                      |                      | ns |
| Negative                                       | 70 (67.4)            | 136 (65.3)           |    |
| Positive                                       | 34 (32.6)            | 72 (34.7)            |    |
| <i>Staging, n (%)<sup>c</sup></i>              |                      |                      | ns |
| I/II   | 68 (65.3)            | 130 (62.6)           |    |
| III/IVa  | 36 (34.7)            | 78 (37.4)            |    |
| <i>Preoperative CT, n (%)</i>                  |                      |                      | ns |
| Yes  | 6 (5.3)              | 7 (3.2)              |    |
| No   | 98 (94.7)            | 201 (96.8)           |    |

CA carbohydrate antigen; CEA carcinoembryonic antigen; T tumor; CT chemotherapy; ns not significant

<sup>a</sup>Covariate used for propensity scores matching

<sup>b</sup>In LPS group, proportions have been calculated according to number of patients undergoing lymphadenectomy

<sup>c</sup>Defined according to 7th Edition of AJCC Classification

22.1%,  $p = 0.02$ ). Liver-related specific morbidities were biliary fistula in three versus seven cases (3.2% vs. 3.7%) and transient liver failure in three versus seven cases (3.2% vs. 3.7%), whereas two versus seven cases of lymphatic fistula (16.8% vs. 22.1%) were responsible of three versus ten (3.2% vs. 5.3%;  $p = 0.05$ ) lymphadenectomy-related complications (Fig. 2). Overall, minor complications according to Clavien–Dindo grade I + II were 12 versus 34 (11.6% vs. 16.3%); major complications grade III + IV were 5 versus 12 (5.3% vs. 5.8%). Mortality rate were comparable between the two series (1.1% vs. 1.1%). Table 5 reports postoperative outcomes specifically in patients with chronic liver disease (respectively 26 in the

MILS and 49 in the Open group). In this subgroup of patients, the incidence of both overall (19.2% and 24.5% in the MILS and Open groups respectively;  $p = 0.03$ ) and lymphadenectomy-related (3.8% and 8.2% in the MILS and Open groups respectively;  $p = 0.03$ ) complications was reduced in patients operated by laparoscopic approach.

Number of retrieved nodes was eight versus seven ( $p =$  not significant); particularly, percentage of patients who achieved the recommended AJCC cutoff of six lymph nodes harvested were 93.7% versus 85.8% ( $p = 0.05$ ). While there was no documented learning curve effect in terms of number of retrieved nodes, the Cumulative Sum (CUSUM) analysis method for time required for

**TABLE 3** Intra- and postoperative details

|   | MILS group (n = 104) | Open group (n = 208) | p    |
|---|----------------------|----------------------|------|
| <i>Procedure, n (%)<sup>a</sup></i>             |                      |                      | ns   |
| Minor resection                                 | 85 (82.1)            | 166 (80)             |      |
| Major resection                                 | 19 (17.9)            | 42 (20)              |      |
| <i>Pringle Maneuver, n (%)</i>                  |                      |                      | 0.04 |
| Not performed                                   | 6 (5.3)              | 24 (11.6)            |      |
| Performed                                       | 98 (94.7)            | 184 (88.4)           |      |
| <i>Length of surgery (min)</i>                  |                      |                      |      |
| Median (range)                                  | 240 ± 55             | 210 ± 60             | ns   |
| <i>Time for liver resection (min)</i>           |                      |                      |      |
| Median (range)                                  | 130 ± 40             | 110 ± 55             | ns   |
| <i>Time for lymphadenectomy (min)</i>           |                      |                      |      |
| Median (range)                                  | 45 ± 35              | 30 ± 25              | 0.05 |
| <i>Blood loss (mL)</i>                          |                      |                      |      |
| Median (range)                                  | 200 ± 100            | 350 ± 250            | 0.03 |
| <i>Number of retrieved nodes</i>                |                      |                      |      |
| Median (range)                                  | 8 (5-11)             | 7 (5-14)             | ns   |
| <i>Harvested nodes &gt; 6, n (%)</i>            | 97 (93.7)            | 178 (85.8)           | 0.05 |
| <i>Surgical margin, n (%)</i>                   |                      |                      | ns   |
| R0  | 101 (96.8)           | 199 (95.8)           |      |
| R1  | 3 (3.2)              | 9 (4.2)              |      |
| <i>Conversion, n (%)</i>                        | 11 (10.5)            | n.a.                 |      |
| <i>Surgical margin (mm)</i>                     |                      |                      |      |
| Mean ± SD                                       | 9 ± 4                | 11 ± 4               | ns   |
| <i>Intraoperative blood transfusions, n (%)</i> |                      |                      | 0.05 |
| No  | 101 (96.8)           | 192 (92.1)           |      |
| Yes   | 3 (3.2)              | 16 (7.9)             |      |
| <i>Postoperative blood transfusions, n (%)</i>  |                      |                      | 0.04 |
| No  | 94 (90.5)            | 175 (84.2)           |      |
| Yes   | 11 (10.5)            | 33 (15.8)            |      |
| <i>Functional recovery (days)</i>               |                      |                      |      |
| Median (range)                                  | 3 (1-5)              | 4 (3-10)             | 0.05 |
| <i>Length of stay (days)</i>                    |                      |                      |      |
| Median (range)                                  | 4 (2-10)             | 6 (3-21)             | 0.04 |
| <i>Interval surgery-chemotherapy (days)</i>     |                      |                      |      |
| Median (range)                                  | 36 (29-45)           | 49 (36-78)           | 0.03 |

RF radiofrequency; R0 negative resection margin; R1 positive resection margin; ns not significant; n.a. not assessable

<sup>a</sup>Covariate used for propensity scores matching

lymphadenectomy showed that the mean value of time was reached at the tenth case in the laparoscopic group (Fig. 3), documenting a learning curve effect after this threshold.

#### Secondary Endpoint: Long-Term Outcomes

Long-term outcomes are shown in Table 6 and Fig. 4. Median disease-free survival was 33 versus 36 months, and disease recurrence occurred in 45.3% versus 55.3% of patients, presenting as nodal (5.3% vs. 8.9%), intrahepatic

(36.8% vs. 35.2%), and extrahepatic (16.8% vs. 14.2%). Even if not statistically significant, surgical therapy of recurrence was more prone in previous laparoscopic cases than open (10.5% vs. 8.4%,  $p =$  not significant).

Median overall survival was 51 versus 63 months, whereas 24.2% versus 28.4% of patients died within last follow-up, being tumor progression-related death responsible of the majority of deaths.

**TABLE 4** Postoperative morbidity and mortality

|  | MILS group (n = 104) | Open group (n = 208) | p    |
|--|----------------------|----------------------|------|
| <i>Complications, n (%)</i>                      |                      |                      | ns   |
| <i>General and liver-related</i>                 |                      |                      |      |
| Bleeding   | 1 (1.1)              | 3 (1.6)              |      |
| Wound infection                                  | 2 (2.1)              | 4 (2.1)              |      |
| Ileus  | 2 (2.1)              | 5 (2.6)              |      |
| Biliary fistula                                  | 3 (3.2)              | 7 (3.2)              |      |
| Transient liver failure                          | 3 (3.2)              | 8 (3.7)              |      |
| Pleural effusion                                 | 2 (2.1)              | 11 (5.3)             |      |
| Pneumonia  | 1 (1.1)              | 3 (1.6)              |      |
| Fever  | 2 (2.1)              | 7 (3.2)              |      |
| Ascites  | 2 (2.1)              | 5 (2.6)              |      |
| <i>Lymphadenectomy-related</i>                   |                      |                      |      |
| Pancreatitis                                     | 1 (1.1)              | 3 (1.6)              |      |
| Lymphatic fistula                                | 2 (2.1)              | 8 (3.7)              |      |
| Bleeding   | 0 (0)                | 1 (0.5)              |      |
| Vascular injury                                  | 0 (0)                | 0 (0)                |      |
| Biliary injury                                   | 0 (0)                | 1 (0.5)              |      |
| <i>Overall morbidity, n (%)</i>                  | 17 (16.3)            | 46 (22.1)            | 0.02 |
| <i>Lymphadenectomy related morbidity, n (%)</i>  | 3 (3.2)              | 11 (5.3)             | 0.05 |
| <i>Grade of complications, n (%)<sup>a</sup></i> |                      |                      | 0.03 |
| <i>Minor</i>                                     |                      |                      |      |
| I grade  | 4 (4.2)              | 15 (7.4)             |      |
| II grade   | 8 (7.4)              | 19 (8.9)             |      |
| <i>Major</i>                                     |                      |                      |      |
| III grade  | 4 (4.2)              | 9 (4.2)              | ns   |
| IV grade   | 1 (1.1)              | 3 (1.6)              |      |
| <i>Mortality, n (%)</i>                          | 1 (1.1)              | 2 (1.1)              | ns   |

ns not significant

<sup>a</sup>Classified according to Dindo–Clavien classification of surgical complications

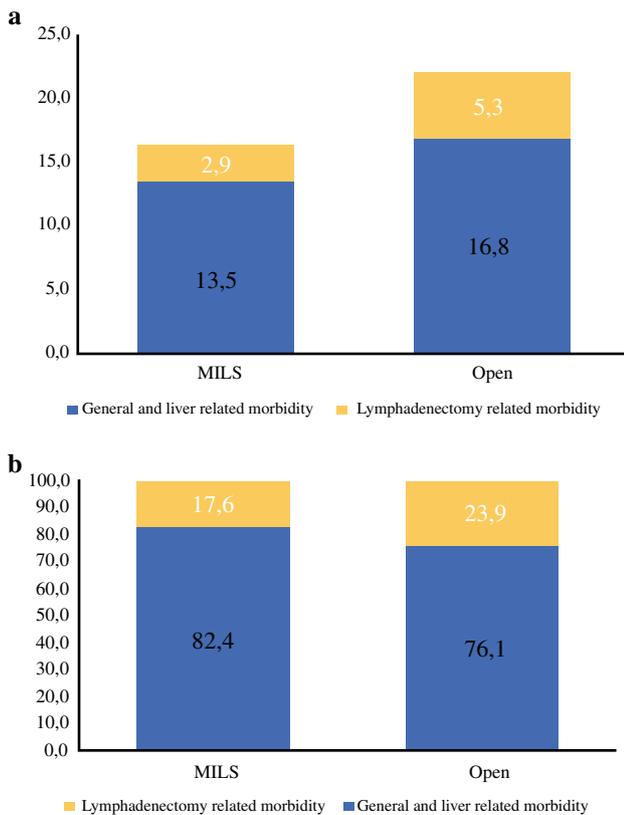
## DISCUSSION

In the present study, matching achieved via the propensity score has allowed to compare patients undergoing open and laparoscopic lymphadenectomy for biliary malignancies overcoming a possible selection bias secondary to a different policy of recruitment in MILS group and constituting the most suitable study design to deepen this debated issue, with the best level of evidence outside of randomization. Randomized, controlled trials (RCTs) are considered as the most appropriate study design, because their power in terms of controlling bias and allowing us to focus very closely on the one intergroup difference of interest are what make them appealing and what lead us to attempt to use this design in all possible situations. In this view, a prospective RCT is advisable even to detect a possible advantage of laparoscopic approach in performing lymphadenectomy for liver malignancies. In the absence of randomization, control for

self-selection can be addressed via statistical methods, so that the notion of matching in retrospective studies was introduced to provide the best level of evidence.

To the best of our knowledge, this is the first series to address the topic of lymphadenectomy, showing that laparoscopic approach is adequate in terms of oncological radicality (median number of retrieved nodes is 8 and 93.7% of patients had more than 6 nodes retrieved) and outcomes (median DFS of 33 months with a rate of nodal recurrence of only 5.3%). Furthermore, it confirmed the benefit of minimally invasiveness on the short-term course of patients who experienced a reduced rate of complications (16.8% and 22.1% in the MILS and Open groups, respectively;  $p = 0.02$ ), especially those specifically related to nodal dissection (3.2% in the MILS and 5.3% in the Open group,  $p = 0.05$ ).

The postoperative gain of the MILS group was detectable both in terms of length of stay and functional recovery and in terms of time between surgery and



**FIG. 2 a** General and liver-related morbidity versus lymphadenectomy related morbidity in the MILS and open series. Percentages are referred to numerosity of study and control groups. **b** General and liver related morbidity versus lymphadenectomy related morbidity in the MILS and open series. Percentages are referred to number of cases with complications in each group

subsequent adjuvant treatments, presumably being even the demonstration of a faster return to autonomy, physical wellness and social life, as documented in the setting of colorectal liver metastases.<sup>19</sup> Reduced need for analgesics, faster mobilization, and autonomous self-care and earlier discontinuation of intravenous fluids, as suggested by fast track management protocols, which were initially introduced in the context of minimally invasive surgery but the adopted even in open resections, allow a reduction of biological and surgical stress of laparoscopy and constitute the bases for a more effective functional recovery.<sup>20,21</sup>

The role of upfront lymphadenectomy in the treatment of primary biliary malignancies is still controversial. Although the presence of nodal metastases is recognized as a negative prognostic factor, recent data show that only 55% of resected patients are submitted to pathologic evaluation of at least one regional node.<sup>22–24</sup> On the other side, the incidence of nodal involvement is significant, because almost 40% of patients are found to have N1 disease.<sup>22–24</sup>

A large variability in lymphadenectomy among Eastern and Western countries is recorded but, according to the eighth edition of the AJCC staging manual, a removal of at least six lymph nodes is suggested for ICC surgery.<sup>25</sup> Bagante et al.<sup>25</sup> evaluated the long-term outcome in a series of 515 patients who underwent lymphadenectomy for ICC when the number of nodes was  $\geq 6$  or  $< 6$ . Authors reported that the cutoff of six harvested nodes has an impact on long-term prognosis of N0 patients—and that the 5 years OS in N0 patients improved with increasing number of nodes—while in N1 patients the number of metastatic nodes rather than the number of retrieved nodes is associated with long-term survival. In fact, the highest accuracy in discrimination between patients with favorable or dismal prognosis was reached when  $\geq 6$  nodes were harvested.<sup>25</sup> In the present series, 93.7% and 85.8% respectively in the MILS and Open groups had more than six nodes harvested, witnessing a possible increased accuracy of minimally invasive approach in achieving an adequate lymphadenectomy. Although minimally invasive lymphadenectomy has always been considered a challenging procedure (in particular more complex compared with the open approach), it can be speculated that the magnification of images gained by laparoscopy together with increase practice in this field, allows to overcome technical difficulties and to obtain a more precise and cautious dissection, identifying correct planes and avoiding injuries to surrounding structures. Furthermore, the availability of modern surgical instruments for sealing and cutting has increased the performance in terms of hemostasis and lymphatic vessels sealing, without negatively affecting the incidence of burn injuries of vascular or biliary branches. It is possible that, widening the sample series, the performance benefit could arise with a statistically significant difference.

Until now, no other specific literature is available to deepen the topic of laparoscopic versus open lymphadenectomy for liver tumors, but the same concerns were raised for nodal dissection in gastric cancers: most series report a comparable number of collected lymph nodes, while interestingly some studies document the possibility of a more extended dissection with an higher number of nodes retrieved in the laparoscopic versus open approach, especially when stations 7 and 8 were considered.<sup>26,27</sup> In addition, a comparable incidence of lymphadenectomy related complications was evidenced in a meta-analysis, including data from 2000 patients and in a case control study in a wide series of 266 patients.<sup>28,29</sup>

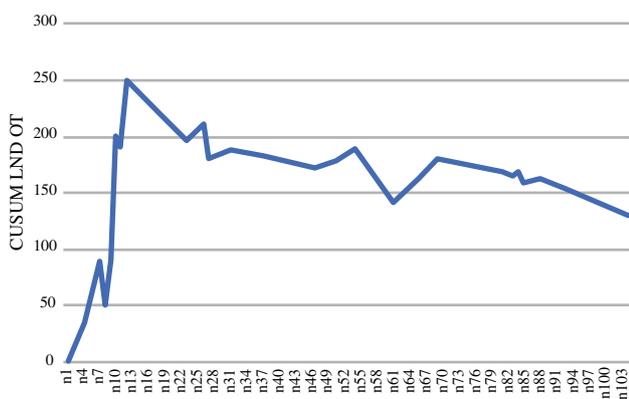
Most open series analyzing the topic of lymphadenectomy in liver surgery do not report a significant incidence of complications specifically related to nodal dissection (lymphatic fistula, bleeding, pancreatitis, vascular, or biliary injuries); despite this, a recent report described an

**TABLE 5** Postoperative morbidity and mortality in patients with underlying liver disease (steatosis, fibrosis or cirrhosis)

|  | MILS group (n = 26) | Open group (n = 49) | p    |
|--|---------------------|---------------------|------|
| <i>Complications, n (%)</i>                      |                     |                     | ns   |
| <i>General and liver-related</i>                 |                     |                     |      |
| Bleeding   | 0 (0)               | 1 (2.0)             |      |
| Wound infection                                  | 0 (0)               | 0 (0)               |      |
| Ileus  | 1 (3.8)             | 0 (0)               |      |
| Biliary fistula                                  | 1 (3.8)             | 2 (4.1)             |      |
| Transient liver failure                          | 2 (7.7)             | 3 (6.1)             |      |
| Pleural effusion                                 | 1 (3.8)             | 4 (8.2)             |      |
| Pneumonia  | 0 (0)               | 0 (0)               |      |
| Fever  | 0 (0)               | 1 (2.0)             |      |
| Ascites  | 2 (7.7)             | 4 (8.2)             |      |
| <i>Lymphadenectomy-related</i>                   |                     |                     |      |
| Pancreatitis                                     | 1 (3.8)             | 2 (4.1)             |      |
| Lymphatic fistula                                | 0 (0)               | 2 (4.1)             |      |
| Bleeding   | 0 (0)               | 0 (0)               |      |
| Vascular injury                                  | 0 (0)               | 0 (0)               |      |
| Biliary injury                                   | 0 (0)               | 0 (0)               |      |
| <i>Overall morbidity, n (%)</i>                  | 5 (19.2)            | 12 (24.5)           | 0.03 |
| <i>Lymphadenectomy related morbidity, n (%)</i>  | 1 (3.8)             | 4 (8.2)             | 0.03 |
| <i>Grade of complications, n (%)<sup>a</sup></i> |                     |                     |      |
| <i>Minor</i>                                     |                     |                     |      |
| I grade  | 0 (0)               | 2 (4.1)             | ns   |
| II grade   | 4 (15.4)            | 6 (12.2)            |      |
| <i>Major</i>                                     |                     |                     |      |
| III grade  | 1 (3.8)             | 3 (6.1)             | 0.04 |
| IV grade   | 0 (0)               | 1 (2.0)             |      |
| <i>Mortality, n (%)</i>                          | 0 (0)               | 1 (2.0)             | ns   |

ns not significant

<sup>a</sup>Classified according to Dindo–Clavien classification of surgical complications



**FIG. 3** Cumulative sum for LND operative time (CUSUM LND OT) plotted against case number

increased risk of postoperative complications in patients undergoing lymphadenectomy who had concomitant cirrhosis, which is a possible situation also in patients developing cholangiocellular neoplasms (1 in 10

patients).<sup>30</sup> In the present study, cirrhosis was present in 10.5% and 8.4% in the MILS and Open groups respectively (resembling the above cited proportion), whereas 14.7% and 15.3% had steatosis or mild liver impairment. Despite the study was not designed to address this topic, Table 5 reports the comparative results specifically in patients with chronic liver disease and highlights a benefit of MILS both in terms of overall (19.2% vs. 24.5% in MILS and Open groups respectively,  $p = 0.03$ ) and lymphadenectomy-related morbidity (3.8% versus 8.2% in MILS and Open groups respectively,  $p = 0.03$ ). It can be argued that analysis of outcomes in a larger sample, with a consequently higher number of patients with cirrhosis, could demonstrate, with adequate level of evidence, benefits associated with laparoscopy comparable to those of patients with hepatocellular carcinoma.

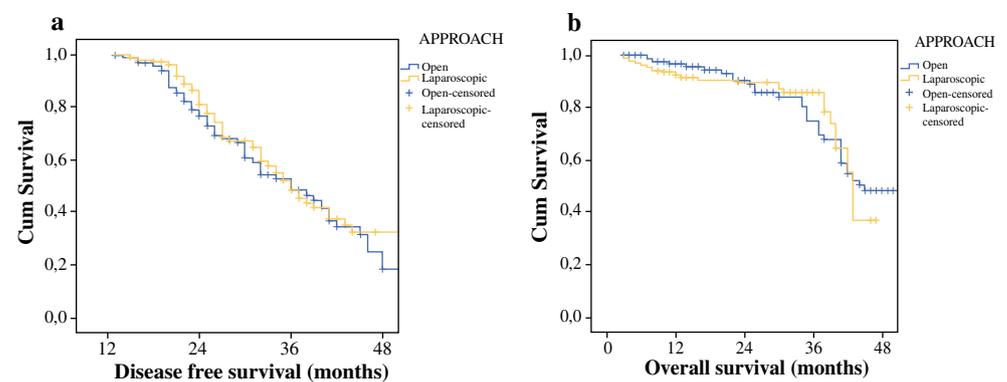
Only recently laparoscopic approach has been considered an option suitable for patients with intrahepatic cholangiocarcinoma and gallbladder cancer. The presence

**TABLE 6** Long-term outcomes

|                                      | MILS group ( <i>n</i> = 104) | Open group ( <i>n</i> = 208) | <i>p</i> |
|--------------------------------------|------------------------------|------------------------------|----------|
| <i>Overall survival (mo)</i>         |                              |                              |          |
| Median (range)                       | 51 (17-62)                   | 63 (17-75)                   | ns       |
| Death <i>n</i> (%)                   | 25 (24.2)                    | 59 (28.4)                    | ns       |
| <i>Cause of death n (%)</i>          |                              |                              |          |
| Tumor progression                    | 25 (24.2)                    | 57 (27.4)                    |          |
| Other                                | 0 (0)                        | 2 (1.1)                      |          |
| <i>Disease free survival (mo)</i>    |                              |                              |          |
| Median (range)                       | 33 (16-45)                   | 36 (13-74)                   | ns       |
| Disease recurrence <i>n</i> (%)      | 47 (45.3)                    | 105 (55.3)                   | ns       |
| <i>Modality of recurrence, n (%)</i> |                              |                              |          |
| Nodal                                | 6 (5.3)                      | 19 (8.9)                     | ns       |
| Intrahepatic, monofocal              | 13 (12.6)                    | 31 (14.7)                    | ns       |
| Intrahepatic, multifocal             | 25 (24.2)                    | 43 (20.5)                    | ns       |
| Extrahepatic                         | 17 (16.8)                    | 30 (14.2)                    | ns       |
| <i>Therapy of recurrence, n (%)</i>  |                              |                              |          |
| Re-resection                         | 11 (10.5)                    | 17 (8.4)                     | ns       |
| Medical therapy                      | 36 (34.7)                    | 87 (41.6)                    | ns       |
| Other local treatments               | 15 (14.7)                    | 11 (5.3)                     | 00.05    |

ns not significant

**FIG. 4** a Disease-free survival.  
b Overall survival



of huge masses requiring major resections or vascular or biliary reconstructions, and secondly, the necessity to guarantee an adequate nodal harvesting have traditionally constituted exclusion criteria of patients affected by cholangiocarcinoma from minimally invasive programs. Cholangiocarcinoma still constitutes a relatively small proportion of patients in large laparoscopic series.<sup>31</sup> In the first report from the Italian Group of MILS (I Go MILS) prospective registry, cholangiocarcinoma constituted the 5.1% of the whole series (82 of 1612 cases) and the 6.5% among cases with malignant disease.<sup>32</sup> Furthermore, in the recent Consensus Guidelines for Laparoscopic Liver Surgery no specific indications were furnished regarding cholangiocarcinoma nor lymphadenectomy, witnessing that laparoscopy still cannot be considered a standard to perform these kind of procedures.<sup>33</sup> A preliminary

experience from our group on 20 laparoscopic cases, which were compared with 60 open cases showed less blood loss (200 vs. 350 mL,  $p = 0.040$ ).<sup>14</sup> Despite less extensive use of the Pringle maneuver, there was no difference in peri-operative morbidity and mortality rates and oncological outcomes were similarly adequate. Based on that, our group progressively widened indications to MILS approach, encompassing even patients with more advanced disease—and therefore requiring more complex resections—and patients with gallbladder cancer. Indeed, favorable results of MILS, together with acquired feasibility of laparoscopic lymphadenectomy and progressively advanced technical skills, have enhanced the commitment toward mini-invasive treatments.

Despite beyond study goals, limiting the possibility to draw strong conclusions regarding specific learning curves and acquisition of techniques for performing laparoscopic LND as required by patients with biliary malignancies, CUSUM analysis revealed a learning curve effect in terms of reduction of operative time required for LND after ten cases. On the contrary, no learning curve effect was recorded in terms of number of retrieved node, which still constitutes a main finding, witnessing that the need for training does not impair oncological results. However, this topic could be interestingly addressed in future studies, maybe including multi-institutional experiences.

## CONCLUSIONS

Technical proficiency of laparoscopic liver resection with associated lymphadenectomy allows to extend the adoption of minimally invasive treatments for primary biliary malignancies, maintaining the benefit of a favorable biological scenario compared with the open technique and therefore allowing a reduced rate of complication, a faster functional recovery, and earlier return to adjuvant treatments. In experienced hands and with an adequate surgical and oncological background, nodal dissection is adequate in terms of number of harvested nodes without affecting the risk of lymphadenectomy-related morbidity.

## COMPLIANCE WITH ETHICAL STANDARDS

**DISCLOSURES** 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. Dr. Francesca Ratti, Dr. Guido Fiorentini, Dr. Michele Paganelli, Dr. Marco Catena, and Dr. Luca Aldrighetti have no conflicts of interest to disclose concerning any commercial interest that they may have in the subject of study and the source of any financial or material support.

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