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MINIMALLY INVASIVE VERSUS OPEN LIVER RESECTIONS FOR HEPATOCELLULAR CARCINOMA IN PATIENTS WITH METABOLIC SYNDROME

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Abstract

Objective.—To compare minimally invasive (MILR) and open liver resections (OLR) for hepatocellular carcinoma (HCC) in patients with metabolic syndrome (MS).

Summary background data.—Liver resections for HCC on MS are associated with high perioperative morbidity and mortality. No data on the minimally invasive approach in this setting exist.

Methods.—A multicenter study involving 24 institutions was conducted. Propensity scores were calculated, and inverse probability weighting was used to weight comparisons. Short- and long-term outcomes were investigated.

Results.—996 patients were included, 580 in OLR and 416 in MILR. After weighing, groups were well matched. Blood loss was similar between groups (OLR 275.9±3.1 vs. MILR 226±4.0, p=0.146). There were no significant differences in 90-day morbidity (38.9% vs. 31.9% OLRs and MILRs, p=0.08) and mortality (2.4% vs. 2.2% OLRs and MILRs, p=0.84). MILRs were associated with lower rates of major complications (9.3% vs. 15.3%, p=0.015), post hepatectomy liver failure (0.6% vs. 4.3%, p=0.008) and bile leaks (2.2% vs. 6.4%, p=0.003); ascites was significantly lower at postoperative day 1 (2.7% vs. 8.1%, p=0.002) and day 3 (3.1% vs. 11.4%, p<0.001); hospital stay was significantly shorter (5.8±1.9 vs. 7.5±1.7, p<0.001). There was no significant difference in overall survival and disease-free survival.

Conclusions.—MILR for HCC on MS is associated with equivalent perioperative and oncological outcomes to OLRs. Fewer major complications, post hepatectomy liver failures, ascites and bile leaks can be obtained, with shorter hospital stay. The combination of lower short-term severe morbidity and equivalent oncologic outcomes favor MILR for MS when feasible.

Keywords

Hepatocellular carcinoma; metabolic syndrome; liver resection; non-alcoholic liver disease

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the third leading cause of cancer-related deaths worldwide.[1] Despite most HCCs developing in the setting of chronic viral hepatitis and/or alcohol-related liver disease, there has been a recent increase in the incidence of both cirrhosis and HCC related to metabolic syndrome (MS), a growing clinical entity in Western countries including hypertension, dyslipidaemia, obesity, and insulin resistance.[2, 3] Indeed, metabolic syndrome leads to non-alcoholic fatty liver disease (NAFLD), a spectrum of hepatic parenchymal changes ranging from simple steatosis to significant fibrosis and cirrhosis.[4, 5] NAFLD triggers carcinogenesis, which results in a 2–4 fold higher risk of developing HCC than the general population, and a yearly incidence as high as 2.6%.[6]

As surgery remains one of the few potentially curative options for HCC, an increasing number of patients with MS are considered for resection, especially in North America and Europe.[7–9] Liver surgery for HCC patients with MS is associated with an up to three-fold risk of mortality and a two-fold risk of morbidity depending on the severity of patients' comorbidities and parenchymal changes.[8, 10–12] In this setting, strategies to decrease the impact of surgery on such complex patients are warranted. Minimally invasive liver resections (MILR) have gained widespread popularity due to the decreased morbidity, length of hospital stays, pain, and more rapid recovery compared to the open approach. Indeed, extensive clinical research, including randomized controlled trials, have disclosed the safety and the advantages of MILR for both benign and malignant diseases, with significant improvements reported over time.[13, 14] Despite this, no data on MILRs for HCC in patients with MS have been described so far. These patients are likely to benefit from a mini-invasive approach but are frequently obese and have multiple comorbidities, which might limit the application of laparoscopy or robotics.

This study aimed to review a large Western experience of MILRs for HCC in patients with MS and to compare it to the open approach. Short-term and oncological outcomes were compared to assess surgical safety and oncological adequacy.

MATERIAL AND METHODS

Study population

Data from 24 institutions (12 European and 12 North American) with experience in the treatment of hepatobiliary malignancies were collected from November 1992 and May 2021. All centers involved in this study are experienced in minimally invasive liver resections, have an established minimally invasive program and are contributing to national registries. Based on volume of patients provided, centers were categorized in high volume (more than 70 patients), medium volume (between 30 and 70 patients), low volume (fewer than 30 patients). Patients with metabolic syndrome undergoing pure laparoscopic, robotic-assisted, or open liver resection for histologically proven hepatocellular carcinoma were included. Metabolic syndrome was defined by 3 out of 5 of the following criteria:[15, 16] a) abdominal obesity (BMI>28.8 kg/m^2 or waist circumference >102 cm in men and >88 cm in women);[17] b) triglycerides >150 mg/dl; c) high-density lipoprotein cholesterol <40 mg/dl in men and <50 mg/dl in women); d) type 2 diabetes or glucose intolerance (fasting glucose >110 mg/dl); e) hypertension (blood pressure >130/85 mmHg). Patients with viral, alcoholic, autoimmune disease, hemochromatosis, and Wilson's disease were excluded as well as cases of fibrolamellar or mixed hepatocellular-cholangiocellular histopathology. Patients with extrahepatic disease or requiring vascular and/or biliary reconstructions were also excluded.

The primary endpoint was the short-term outcome, focusing on 90-day postsurgical morbidity and mortality. Secondary endpoint was the long-term oncological outcome, including survival and disease-free survival.

Institutional Review Board (IRB) approval was obtained from the coordinating center (n° 16–801, approved December 7th, 2020). Data transfer agreement and IRB approval were included and requested by all participating institutions. Every case was discussed in a multidisciplinary setting according to the centers' policies.

Both laparoscopic and robotic-assisted procedures were included in the MILR group. Procedures converted to open were analysed in the MILR group following an intention-to-treat policy. Portal hypertension was defined as the radiological presence of significant splenomegaly, umbilical vein recanalization, and/or portosystemic shunts as well, as preoperative platelets count <100,000/mm^3.[18] Major liver resections were defined as the resection of 3 segments or more according to the Brisbane 2000 nomenclature and the "New World Terminology" of hepatectomies.[19, 20] Liver segments II-III-Ivb-V and VI were defined as anterolateral while segments I-IVa-VII and VIII as posterosuperior.[21, 22] Morbidity was graded according to the Clavien-Dindo classification and the Comprehensive Complication Index.[23, 24] Complications of grade 3 or higher according to Clavien-Dindo classification were considered major morbidity. Postoperative ascites was characterized by a drainage output of more than 10 mL/kg/24h.[25] Post hepatectomy liver failure (PHLF) and bile leakage were graded according to the International Study Group on Liver Surgery definition.[26, 27]

Statistical analysis

Variable's distribution was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Quantitative data were expressed as mean and standard deviation (sd) or median and first and third quartile (Q1-Q3) as needed, for variable needing a logarithmic transformation, the geometric mean (GM) was reported to present data in the original unit measure. Categorical data were expressed as numbers and percentages (%). The chi-squared test was used to compare differences between categorical variables.

To account for the baseline imbalance of the two groups, propensity scores (PS) were calculated for each patient. The propensity score represented the predicted probability of receiving MILR and was determined using a multivariable logistic regression model using as the independent variables confounders related to both the exposure and the outcome selected a priori based on background knowledge. The model included the following variables: year of operation (2001–2015, 2016–2021), age, gender, BMI (<24.9, 25–29.9, ≥30), comorbidities, cirrhosis, the model for end-stage liver disease (MELD), previous HCC treatment (no treatment, locoregional, resection), the position of lesions (anterolateral, left lobe, posterosuperior, right lobe), number and size of lesions, previous surgery, type of hepatectomy (minor, major), and geographic area (Europe, North America). Inverse probability weight (IPW) was calculated for each patient and used to weight the analysis. Standardized differences (STD) calculated in unweighted and weighted samples were used to assess the balance of baseline covariates between the two groups. Stabilized weights were used to handle very small or very large propensity scores. An STD value ≤0.1 was considered a good balancing. Associations between the type of surgery and outcomes were investigated by weighted logistic, negative binomial, Poisson, and linear regression depending on the outcome variable. Long-term Overall survival (OS) and disease-free survival (DFS) were estimated using weighted Kaplan–Meier curves, and comparisons were performed with weighted Cox Regressions. OS was defined as the time interval from surgery to death for any cause or last follow-up while DFS as the interval from surgery to recurrence in the liver or elsewhere or the date of the last follow-up.

A $p<0.05$ was considered significant. Statistical analysis was performed with STATA version 16.1 (StataCorp, College Station, TX, USA).

RESULTS

A total of 1100 liver resections for HCC on metabolic syndrome were collected and reviewed. Because no minimally invasive procedures were performed before 2001, 13 patients operated on by open between 1992 and 2001 were excluded from the study. Furthermore, 91 patients were excluded because they had at least one missing value in the variables used to calculate the propensity scores. The final sample of the study consisted of 996 patients, 580 OLR (58.2%) and 416 (41.8%) MILR (Figure 1). Within the MILR group, 353 resections (85.0%) were performed by pure laparoscopy, 52 (12.5%) by hand-assisted laparoscopy, and 11 (3.0%) by robotics. Baseline characteristics before and after inverse probability weighting are depicted in Table 1. In the OLR group there were more patients with diabetes (59.5% vs. 52.6%, STD −0.14) and with a history of ischemic heart disease (22.2% vs. 15.9%, STD −0.16). In comparison, more patients with previous respiratory disease were operated on by minimally invasive approach (18% vs. 13.8%, STD 0.12). A greater proportion of cirrhotic patients were operated on by MILR (42.8% vs. 31.2%, STD 0.24). Tumors in the MILR group were smaller (40 mm (27–56) vs. 55 mm (36–85), STD −0.50) and more likely to be in the anterolateral segments of the liver (56.5% vs. 37.6%, STD 0.39). Minor hepatectomies were more common in MILR (80.3% vs. 60.9%, STD 0.44). while most of the major hepatectomies were performed by open (39.1% vs. 19.7%, STD −0.44). After inverse probability weighting, the above-mentioned differences were corrected, and the two groups were well balanced (Table 1). Furthermore, there were no significant differences in the two groups in additional baseline, intraoperative, and pathological characteristics (Supplementary table 1).

During surgery, blood loss weighted geometric mean was 275.9 ml (±3.1) in OLR and 226.9 ml (±4.0) in MILR (p=0.146) with 12.2% and 13.1% of patients receiving intraoperative blood transfusions in OLR and MILR respectively (p=0.785). There were no significant differences in terms of any 90 day morbidity (38.9% vs. 31.9% OLRs and MILRs, p=0.08) and mortality (2.4% vs. 2.2% OLRs and MILRs, p=0.84) between groups (Table 2). However, MILRs were associated with lower rates of major complications (9.3% vs. 15.3%, p=0.015), post hepatectomy liver failure (0.6% vs. 4.3%, p=0.008) and bile leaks (2.2% vs. 6.4%, p=0.003). Furthermore, ascites was significantly lower at postoperative day 1 (2.7% vs. 8.1%, p=0.002) and day 3 (3.1% vs. 11.4%, p<0.001). No further differences in specific complications were observed (Supplementary table 2). Finally, hospital stay was significantly shorter in MILR (5.8±1.9 days vs. 7.5±1.7 days, p<0.001). Oncologic outcomes were similar between both approaches. There was no difference in margin positivity rates between OLR and MILR (7.6% and 11.6% respectively; p=0.179). After a median follow-up of 33 (15–59) months for OLR and 31 (16–64) months for MILR, there were also no significant differences in overall survival between groups (HR=0.90, 95% CI 0.69–1.19, p=0.461). Five years overall survival rate was 58.2% in OLR and 60.8% in MILR (Figure 2). Overall, 460 patients (46.1%) recurred after resection, 297 in open and 163 in the minimally invasive group. There were no significant differences in disease-free survival between groups (HR=0.84 95% CI 0.66–1.06 p=0.138). Five years disease-free survival rate was 39.3% in OLR and 47.8% in MILR (Figure 3).

DISCUSSION

In this study, we have shown that compared to OLR, MILR for patients with HCC and MS is associated with lower rates of major complications, post hepatectomy liver failure, ascites, bile leaks, and shorter hospital stay. Furthermore, MILR was associated with similar long-term oncologic outcomes to OLR.

Because of the high calorie-low fiber diet and the scarce physical activity, a growing number of patients with metabolic syndrome and NAFLD have been diagnosed with HCC and are increasingly being considered for surgery, especially in the West. Liver resections in these patients bear high rates of perioperative morbidity and mortality, and strategies to decrease the risks of surgery are warranted.[28, 29] Minimally invasive approaches are safely performed in many hepatobiliary centers worldwide. Indeed, two International consensus conferences, one European guideline, and one dedicated society (the International laparoscopic liver society, ILLS) facilitated the safe implementation and standardization of the technique over the years.[13, 30–32] Given this global success, MILRs have been successfully adopted under challenging scenarios such as unfavorable locations, advanced cirrhosis, liver transplantation, and resection for recurrent tumors, challenging the limits of the technique and expanding the commonly accepted indications.[21, 33–36] In general, patients with HCC and MS represent a complex clinical scenario, and minimally invasive liver resections in this setting could be at high risk of perioperative complications. Indeed, these patients are frequently obese, have multiple comorbidities, different degrees of portal hypertension, and underlying parenchymal changes (i.e., steatosis, fibrosis, cirrhosis). In our study, most patients were overweight (BMI ≥25 kg/m^2) or obese (BMI ≥30 kg/m^2) and had preexisting cardiovascular and/or respiratory conditions. Interestingly, before matching, a greater proportion of cirrhotic patients were operated on in the MILR group. Morise et al. and Cipriani et al. have previously demonstrated that minimally invasive approach for HCC allows expanding the indications to patients with advanced cirrhosis given the reduced surgical stress and the lower chances of postoperative decompensation.[37, 38] In this setting, it seems reasonable that surgeons might have preferred a minimally invasive approach in cirrhotic patients, to potentially decrease the rates of postoperative morbidity, thereby explaining this imbalance before matching in our study. Despite this, MILRs remain technically more challenging, and easier resections are usually attempted relative to those performed using an open approach. Indeed, more resections in the anterolateral segments were performed by MILRs while major hepatectomies and lesions located posteriorly or superiorly in the so-called unfavorable segments were more commonly operated on by open techniques. After IPW, the above-mentioned imbalances were corrected, and groups were homogenous. Although the overall morbidity was similar, MILR was associated with fewer major complications. In our opinion, this is an important result as patients who develop high-grade complications require invasive intervention, significantly impacting hospital stay, costs, quality of life, and potentially delaying oncological treatments. In addition, complications have been associated with worse long-term oncologic outcomes.[39] Reducing the rates of major complications translates into reduced hospital costs and better patient outcomes, both in the short- and long-term. Patients' decompensation following surgery for HCC is not uncommon and depends on the degree of portal hypertension and preoperative liver conditions. Indeed, adaptations of the portosystemic circulation induced by the altered intrahepatic pressures lead to a fragile equilibrium that can be potentially dismantled with surgery, eventually leading to decompensation. In this study, we have shown that MILR allows respecting this equilibrium, decreasing the rates of post hepatectomy liver failure and the production of ascites. Surgical stress is significantly reduced, portosystemic shunts are respected, extensive liver mobilizations and manipulations are avoided, the abdominal content is not exposed to the air, and less fluids are required, limiting electrolyte imbalances.[40] The rates of bile leaks were also reduced in MILR. This may be related to the magnified vision provided by laparoscopic and robotic surgery platforms. This may assist in identifying small structures, allowing the surgeon to be more selective during parenchymal transection. Nowadays, this is further enhanced by technologies such as high definition, 4K, 3D, near-infrared light, and indocyanine green dye. Accurate parenchymal transection and biliostasis allow for opportunities to reduce postoperative bile leaks, bilomas, and eventually major morbidity and invasive procedures.

MILRs are associated with safe oncological outcomes for the treatment of both primary and secondary liver malignancies.[41, 42] This has been confirmed in prospective randomized control trials for CRLM and HCC.[43, 44] The results of MILRs for HCC in patients with MS have never been investigated. Authors suggest that survivals in this setting are better than those in viral or alcoholic diseases, probably because fewer patients present with cirrhosis and impaired liver function.[29, 45] Indeed, NAFLD triggers carcinogenesis, and many patients with MS develop HCC in the absence of cirrhosis. In the present study, we confirm the good survival results of this subset of patients, even when treated by minimally invasive technique. Indeed, 61% of patients were alive, and 48% were disease-free at five years. Importantly, these results were comparable to OLR.

This study has some limitations. The retrospective design might have introduced selection bias. Indeed, this is a cohort of surgical candidates while patients with advanced disease, major comorbidities, or advanced cirrhosis were likely to be excluded. Intention-to-treat studies investigating unselected patients are warranted as they could be informative of the process of selection for both open and minimally invasive surgery. The MILR group of our study was composed of patients undergoing pure laparoscopic, hand-assisted, and robotic liver resections. Despite these being all minimally invasive procedures and having overall comparable short and long-term outcomes, minor differences should be considered when interpreting results. Hand-assisted procedures are used at the beginning of the learning curve as a gradual shift from open to laparoscopy and still represent the preferred approach in a few centers. On the contrary, the experience in robotic surgery is growing rapidly, with exciting results compared to laparoscopy.[46] Comparisons with laparoscopy in the setting of MS are warranted and could be of great interest. A recent definition of metabolic-associated fatty liver disease (MAFLD) was proposed:[47, 48] unfortunately, collection of data was ongoing when this new definition was proposed. MAFLD should be investigated and validated to standardize terminology among the literature. The findings of reduced ascites and biliary fistula with MILR of the present study should be interpreted with caution. Indeed, we don't know the exact number of procedures in each group in which drainage was left in place. This can significantly vary between centers and type of resections. Even though inverse probability weighting aims at reducing differences among groups, selection bias at single variable level is not easy to avoid. Pathological differences in T stage and microvascular invasion could confound results, especially survivals, and this should be considered when interpreting results. Finally, this is a Western cohort of patients, and results should not be generalized to Eastern populations in which metabolic syndrome may have a similar prognostic significance but different incidence, risk factors, and pathogenesis.

CONCLUSIONS

Minimally invasive liver resections for hepatocellular carcinoma in patients with metabolic syndrome are associated with comparable overall morbidity,and long-term oncologic outcomes to the open approach. In contrast, minimally invasive liver resections are associated with a significant reduction in major complications, post hepatectomy liver failure, ascites, bile leaks, and shorter hospital stay. The combination of a favorable morbidity profile and equivalent oncologic outcomes favor a minimally invasive surgical approach when feasible for patients with metabolic syndrome. Selection of patients should take into account baseline characteristics, the difficulty of the resection, and surgeon's experience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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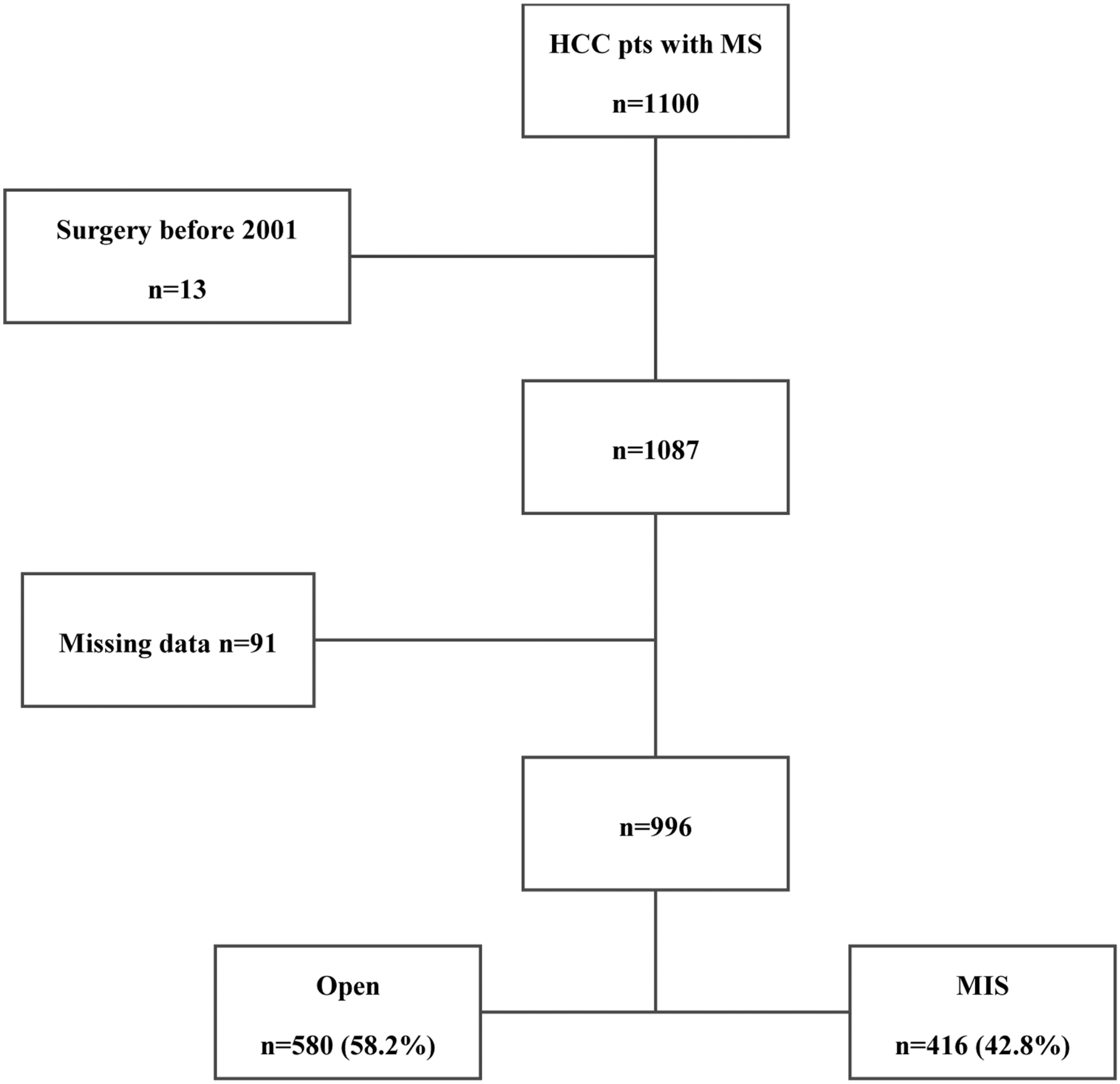

Figure 1.
Flow chart of the patients included in the study.

HCC, hepatocellular carcinoma; MS, metabolic syndrome; MIS, minimally invasive surgery

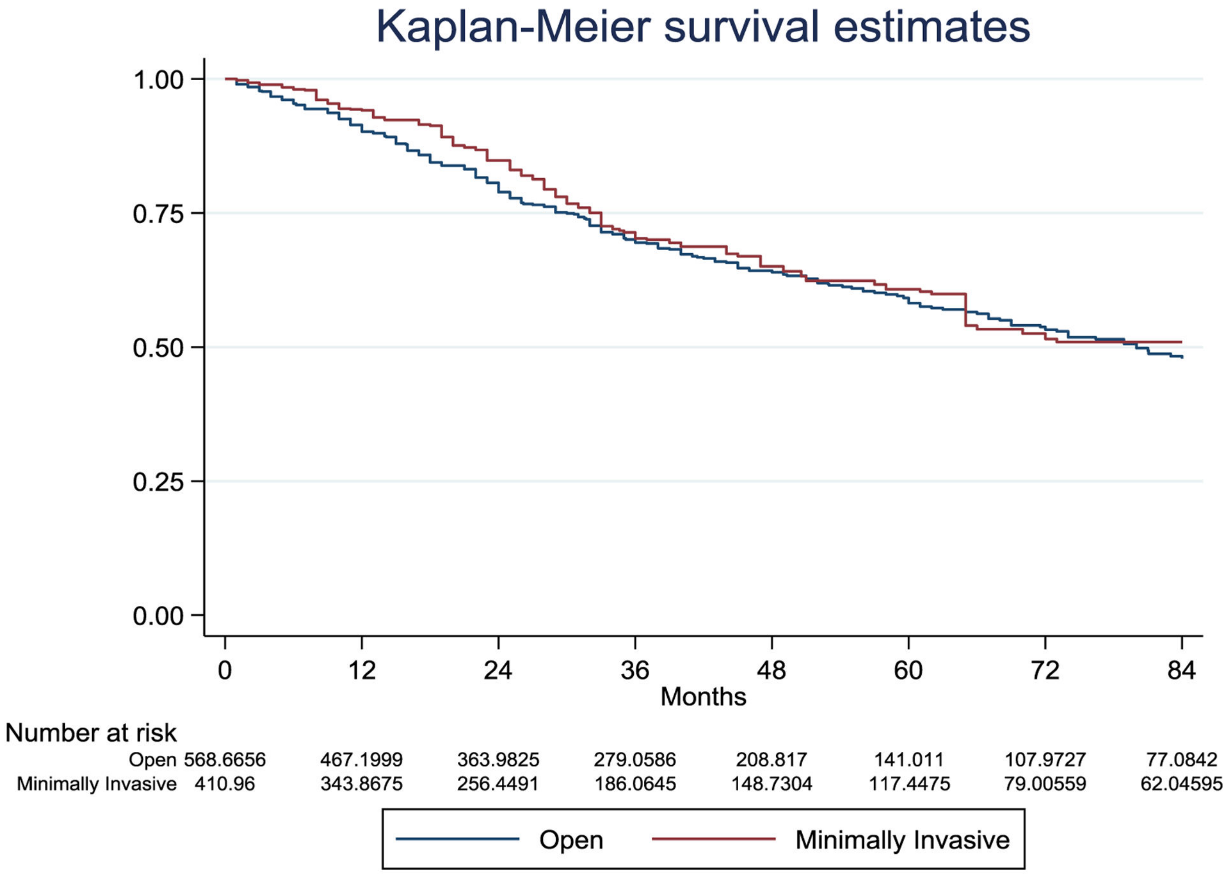

Figure 2.

Inverse probability weighted Kaplan-Meier curves of overall survival according to treatment assignment.

Overall survival HR=0.90, 95% CI 0.69–1.19, p=0.461. Number of patients represent the number in the synthetic pseudo-population generated by the inverse probability treatment weighting

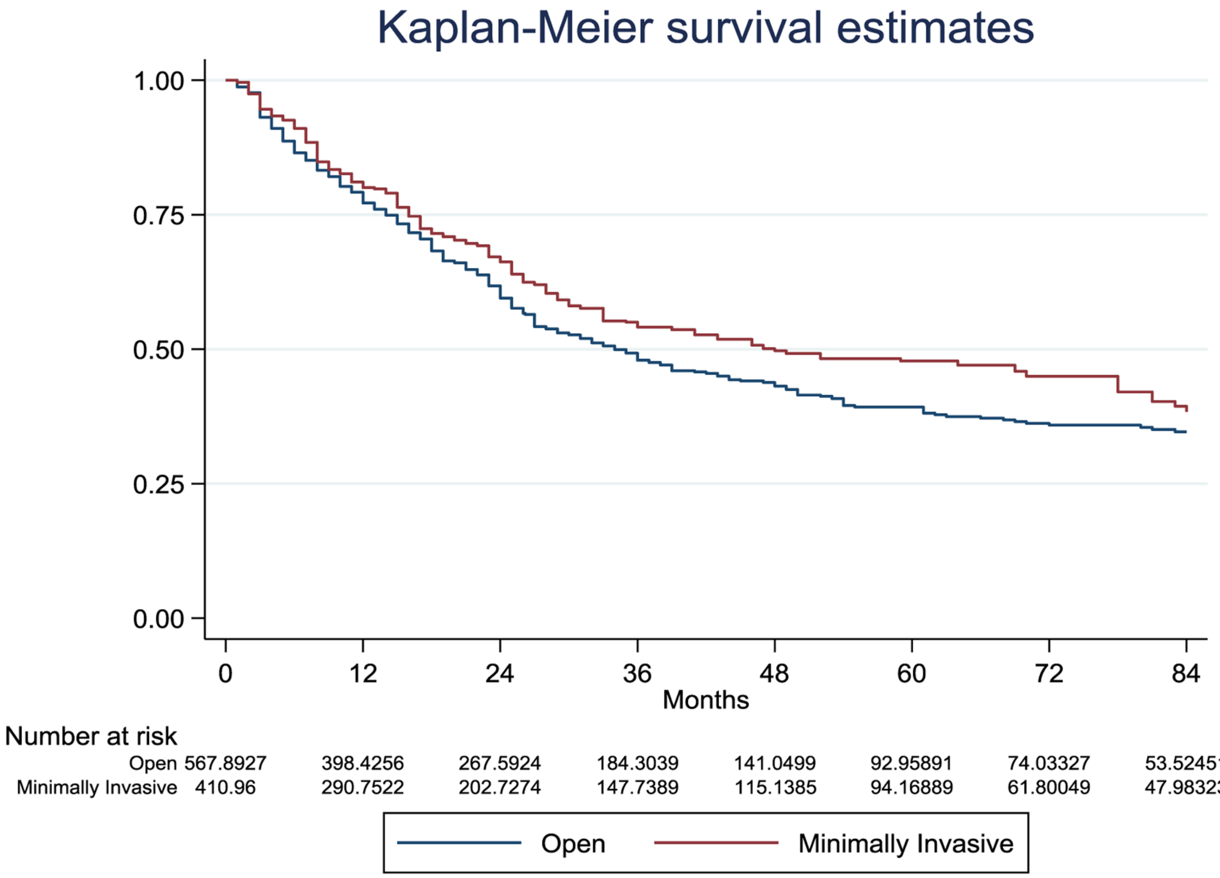

Figure 3.

Inverse probability weighted Kaplan-Meier curves of disease-free survival according to treatment assignment.

Disease free survival HR=0.84 95% CI 0.66–1.06 p=0.138. Number of patients represent the number in the synthetic pseudo-population generated by the inverse probability treatment weighting

Table 1.

Baseline variables used for propensity score in unweighted and weighted populations.

	Unweighted population			Weighted population		
	Open (n=580)	**Minimally Invasive (n=416)**	**Unweighted STD**	**Open (n=580)**	**Minimally Invasive (n=416)**	**Weighted STD**
Age (years)	68.6 (±9.2)	68.9 (±9.0)	0.04	68.7 (9.3)	69.2 (8.9)	0.06
Male gender	422 (72.8%)	293 (70.4%)	−0.05	72.1%	73.1%	0.02
Geographic Area						
Europe	319 (55.0%)	219 (52.6%)	−0.05	56.7%	58.5%	0.04
North America	261 (45.0%)	197 (47.4%)	0.05	43.3%	41.5%	−0.04
Centers' volume						
High	275 (47.4%)	208 (50.0%)	0.05	45.6%	47.1%	0.03
Medium	250 (43.1%)	167 (40.1%)	−0.06	45.0%	42.5%	−0.05
Low	55 (9.5%)	41 (9.9%)	0.01	9.4%	10.4%	0.03
Body mass index						
<24.9 kg/m ^{2}	113 (19.5%)	80 (19.2%)	0.00	19.5%	20.1%	0.01
25–29.9 kg/m ^{2}	204 (35.2%)	158 (38.0%)	0.06	34.8%	36.8%	0.01
≥ 30 kg/m^2	263 (45.3%)	178 (42.8%)	−0.05	45.7%	43.1%	−0.05
Hypertension	462 (79.7%)	314 (75.5%)	−0.01	78.1%	77.9%	0.00
Diabetes	345 (59.5%)	219 (52.6%)	−0.14	57.9%	57.7%	0.00
Ischemic heart disease	129 (22.2%)	66 (15.9%)	−0.16	19.7%	19.4%	−0.01
Congestive cardiac failure	27 (4.7%)	24 (5.8%)	0.05	5.1%	4.7%	−0.02
Respiratory disease	80 (13.8%)	75 (18.0%)	0.12	15.1%	16.9%	0.05
Dyslipidemia	308 (53.1%)	225 (54.1%)	0.02	52.8%	51.6%	−0.02
Previous surgery	99 (17.1%)	74 (17.8%)	0.02	17.9%	19.6%	0.04
Cirrhosis	181 (31.2%)	178 (42.8%)	0.24	34.4%	34.5%	0.00
MELD score	8 (6.4–9)	8 (6–9.4)	0.12	8 (6.4–9.1)	7 (6–9)	−0.01
Previous HCC treatment						
Locoregional	73 (12.6%)	42 (10.1%)	−0.08	86.7%	85.3%	0.05
Resection	14 (2.4%)	9 (2.16%)	−0.02	11.2%	12.7%	−0.01
Year of surgery						
2001–2015	415 (71.6%)	153 (36.8%)	−0.74	57.3%	55.9%	−0.03
2015–2021	165 (28.5%)	263 (63.2%)	0.74	42.7%	44.1%	0.03
Number of lesions	1 (1–1)	1 (1–1)	−0.12	1 (1–1)	1 (1–1)	−0.03
Size of lesions (mm)	55 (36–85)	40 (27–56)	−0.50	50 (32–76)	48 (32–75)	0.04
Position of lesions						
Anterolateral	218 (37.6%)	235 (56.5%)	0.39	44.9%	46.7%	0.04
Left lobe	55 (9.5%)	30 (7.2%)	−0.08	8.6%	9.0%	0.01
Posterosuperior	163 (28.1%)	111 (26.7%)	−0.03	27.6%	25.1%	−0.06
Right lobe	144 (24.8%)	40 (9.6%)	−0.41	18.9%	19.2%	0.01
Type of hepatectomy						
Minor	353 (60.9%)	334 (80.3%)	0.44	68.5%	68.1%	−0.01

	Unweighted population			Weighted population		
	Open (n=580)	**Minimally Invasive (n=416)**	**Unweighted STD**	**Open (n=580)**	**Minimally Invasive (n=416)**	**Weighted STD**
Major	227 (39.1%)	82 (19.7%)	−0.44	31.5%	31.9%	0.01

STD, Standardized differences. **MELD,** Model for End Stage Liver Disease. **HCC,** hepatocellular carcinoma

Table 2.

Regression analysis for postoperative outcomes after inverse probability weighting.

	Open n=580	Minimally invasive n=416	Minimally invasive vs. Open		95% confidence interval	p
90 day mortality	2.4%	2.2%	OR	0.92	0.38–2.22	0.845 [*]
90 day morbidity (any)	38.9%	31.9%	OR	0.73	0.52–1.04	0.081 [*]
Number of complications	0.68 (±1.1)	0.55 (±1.0)	Beta	−0.22	−0.57–0.13	0.218 [-]
Major morbidity	15.3%	9.3%	OR	0.57	0.36–0.90	**0.015** [*]
CCI	31.3 (±22.7)	31.9 (±22.2)	Beta	0.63	−4.73–5.99	0.817 [#]
Postoperative ascites	11.2%	7.2%	OR	0.61	0.28–1.34	0.22 [*]
Post hepatectomy liver failure	4.3%	0.6%	OR	0.14	0.03–0.60	**0.008** [*]
Bile leak	6.4%	2.2%	OR	0.33	0.15–0.69	**0.003** [*]
Postoperative day 1 ascites	8.1%	2.7%	OR	0.31	0.15–0.65	**0.002** [*]
Postoperative day 3 ascites	11.4%	3.1%	OR	0.25	0.12–0.51	**<0.001** [*]
Postoperative day 5 ascites	13.7%	7.2%	OR	0.51	0.17–1.57	0.244 [*]
Hospital stay (days)	7.5 (±1.7)	5.8 (±1.9)	Beta	−0.11	−0.15–0.7	**<0.001** [+]
Readmission within 30 days	8.4%	8.6%	OR	1.02	0.54–1.93	0.956 [*]
R1 resection	7.6%	11.3%	OR	1.55	0.82–2.95	0.179 [*]
Margin width (mm)	3.6 (±7.5)	3.1 (±9.6)	Beta	−0.06	−0.24–0.12	0.497 [+]

Continuous data were expressed as mean±standard deviation or median (25^{th}-75^{th} percentile).

[*] calculated from weighted logistic regression.

[-] calculate from weighted negative binomial regression.

[°] calculated from weighted poisson regression.

[#] calculated from weighted linear regression.

[+] calculated from weighted linear regression on log10 values.

CCI, Comprehensive complication index. **GM,** Geometric mean.