ORIGINAL ARTICLE

Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma: The European experience

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Summary

Purpose: The aim of this meta-analysis of studies conducted in Europe was to evaluate the effect of laparoscopic liver resection (LLR) on short- and long-term outcomes compared to open liver resection (OLR) in patients operated for hepatocellular carcinoma (HCC).

Methods: An electronic literature search was conducted in order to identify studies comparing LLR and OLR. Short-term outcomes evaluated included operative time, blood loss, need for transfusion, R0 resection, resection margin width, length of hospital stay, morbidity and 30-day postoperative mortality. Long-term outcomes included 1-year, 3-year, 5-year overall (OS) and disease-free survival (DFS) as well as tumor recurrence rate. RevMan 5.1 software was utilized for statistical meta-analysis.

Results: A total of 851 patients from 10 European studies were included in the present meta-analysis reporting for short- and long-term results for LLR and ORL for HCC.

Among them 321 (37.7%) underwent laparoscopic hepatectomy and the remaining 530 (62.3%) were operated through open approach. LLR were found to be strongly associated with lower blood loss as well as need for blood transfusion, shorter hospital stay, lower 30-day mortality and morbidity and finally improved 1-year OS and 5-year DFS. Operative time, R0 resection, resection margin width, tumor size, 3- and 5-year OS as well as 1- and 3-year DFS were not found significantly different among the two groups.

Conclusion: The present meta-analysis demonstrates the superiority of laparoscopic over open approach for same sized tumors. Cirrhotic patients benefit from laparoscopy in terms of shorter hospital stay, complication rate and long-term oncologic outcomes.

Key words: Europe, hepatocellular carcinoma, laparoscopy, open, resection

Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and represents a leading cause of death worldwide, being the second most common cause of cancer-related death with an estimated 782,000 new cases and 745,000 deaths in the year 2012 [1,2]. Therapeutic approaches in the management of HCC have evolved rapidly and may include application of improved locoregional therapies, newer targeted systemic therapies, novel techniques for both internal and external radiation therapy, and the possibility of transplantation [3-5]. Nevertheless

surgical resection remains the cornerstone in the therapeutic management of HCC providing the best outcomes for patients eligible for resection. Whatsoever, prognosis for HCC still remains poor, presumably as a result of delayed diagnosis.

The performance of LLR has increased rapidly during the last 20 years. Gagner et al. reported the first LLR in 1992 for a benign lesion [6], whereas the first report on laparoscopic resection for HCC was in 1995 by Hashizume et al. [7]. Inadequacy of suitable laparoscopic tools and lack of laparoscopic expertise in combination with a relatively steep

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learning curve impeded surgeons from embarking on such procedures. Progress of technology on instruments and devices used in laparoscopic surgery as well as laparoscopic proficiency gradually led to a broad performance of LLRs for HCC. LLRs are currently acknowledged as safe procedures with acceptable morbidity and mortality for both minor and major liver resections in the hands of certified hepatobiliary surgeons with experience in laparoscopic surgery [8,9].

Numerous studies and meta-analyses report comparable outcomes of open liver resection (OLR) and LLR as curative options in the management of HCC. The majority of the studies included in those meta-analyses come from Asian liver surgery centers whereas there is no meta-analysis evaluating the results of LLR and ORL in a European population given the fact that Asian patients present substantial differences from Europeans. The aim our meta-analysis was to investigate short and long-term outcomes of LLR vs OLR for HCC from studies conducted in Europe.

Methods

Study design

This meta-analysis was designed according to the PRISMA guidelines, while the authors predetermined eligibility criteria [10].

Three authors independently searched the literature. Language restrictions were applied during the literature search and only English written articles were evaluated for inclusion in our meta-analysis. All prospective and retrospective clinical studies originating from Europe and compared LLR with ORL for HCC were included in the present systematic review. Case reports, reviews and animal studies were excluded from tabulation. All discrepancies during the data collection, synthesis and analysis were resolved by consensus of all authors.

Literature search and data collection

We systematically searched the literature using the Medline, Scopus, and Google Scholar databases for articles published up to June 2016, along with the references of all articles, which were retrieved in full text. Our search included the words "laparoscopy", "laparoscopic", "minimally invasive", "open liver resection", "liver resection", "hepatectomy", "hepatocellular carcinoma", "primary liver cancer", "HCC", "European" and is presented in Figure 1, in the PRISMA flow diagram which depicts the search strategy of article retrieval.

Quality assessment

The quality of all the included studies was assessed using the Newcastle-Ottawa Scale (NOS) [11]. This suggests a quality assessment tool, designed for estimating the methodological adequacy of non-randomized studies. NOS consists a star-based system, which evaluates the selection of the study groups, the comparability of the groups and the ascertainment of the outcome of interest. A maximum of 4, 2 and 3 stars can be attributed to terms of 'Selection', 'Comparability' and 'Exposure' respectively with a maximum number of 9 stars for each individual study. Studies evaluated with a score of 6 or more stars were considered of high quality. We used the NOS, since all the studies included in our meta-analysis were non-randomized.

Statistics

Statistical meta-analysis was performed using the RevMan 5.1 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals (CI) were set at 95%. Mean difference (MD) and odds ratios (OR) were used in the analysis. Firstly fixed effects model was used for all primary and secondary outcomes and in case of heterogeneity (Q test p value < 0.1) the results were calculated using the DerSimonian-Laird random effect model (REM) revealing significant heterogeneity in the methodological characteristics of the included studies [12]. The cut-off for statistical significance was set at p ≤0.05. Heterogeneity and overall effect were both tested for each total and subtotal comparison. To identify sources of heterogeneity, sensitivity analysis was performed.

Definitions

The term of overall morbidity was used in our study to describe the incidence of overall postoperative complications, which were defined in the included studies as the number of patients presented postoperatively with any kind of complication.
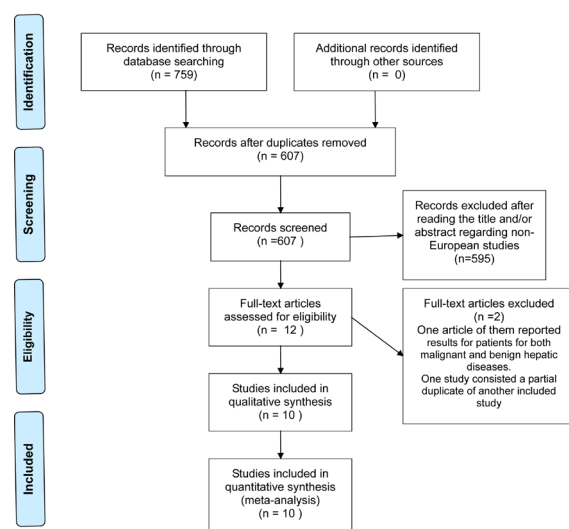

Figure 1. Search flow diagram.

Results

Excluded studies

Our search was based on studies conducted in Europe so as to compare the outcomes of lapa-

roscopic and open hepatectomy in patients that were operated in European Surgical centers. Thus, studies originating from Asia or USA were excluded. Furthermore, among European studies Morino et al. reported data from LLRs for both malignant and benign lesions and were excluded from the analysis [13]. Finally, another study was a partial duplicate of an already included study and was excluded as well from the present analysis [14].
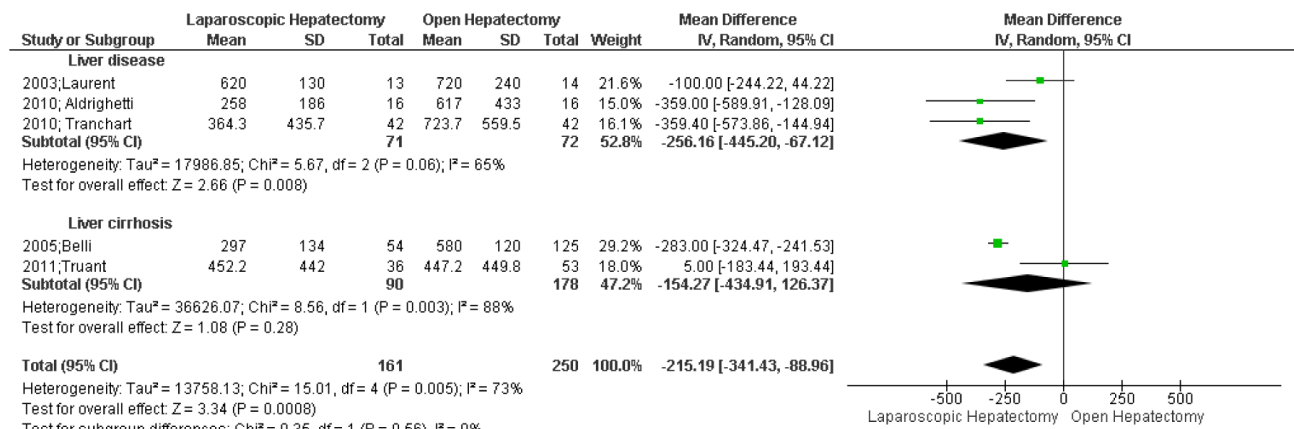
Included studies

Ten studies were finally included in our systematic review, which involved 851 patients [15-24]. Among them, 321 (37.7%) patients had undergone laparoscopic hepatectomy while the remaining 530 (62.3%) formed the open group. The results were analyzed in two separated subgroups. The first one including 251 patients consisted of those with HCC and various liver diseases (cirrhotic and non-cirrhotic), while the second one with 600 patients included only patients with cirrhosis plus HCC. The analyzed indices were tabulated in four structured forms that included the methodological characteristics of the included studies (Table 1), the characteristics of enrolled

patients (Table 2) and the short and long-term outcomes of the operations among the aforementioned groups (Table 3).

Outcomes

Primary and secondary outcomes of included studies are presented in Table 3. We observed that despite the fact that operative time was significantly prolonged in the case of cirrhotic patients with HCC who underwent open hepatectomy when compared with cirrhotic ones operated laparoscopically (cirrhotic subgroup) (424 patients, mean difference (MD) -15.46min, 95% CI-28.34, -2.59, p=0.02), in the case of overall comparison, operative time did not differ among the two groups (567 patients MD -2.60min, 95% CI -33.23, 28.04, p=0.87). On the other hand, patients in the laparoscopy group showed significantly improved intraoperative outcomes concerning blood loss and blood transfusion rates (411 patients, MD-215.19ml, 95% CI -341.43, -88.96 p=0.0008, Figure 2 and 765 patients, odds ratio/OR 0.32, 95% CI 0.19, 0.55, p<0.0001, respectively). In the case of subgroup analysis blood loss was not found different only among cirrhotic patients who under-

Figure 2. Forest plot depicting mean difference (MD) for blood loss (ml) in the included studies.
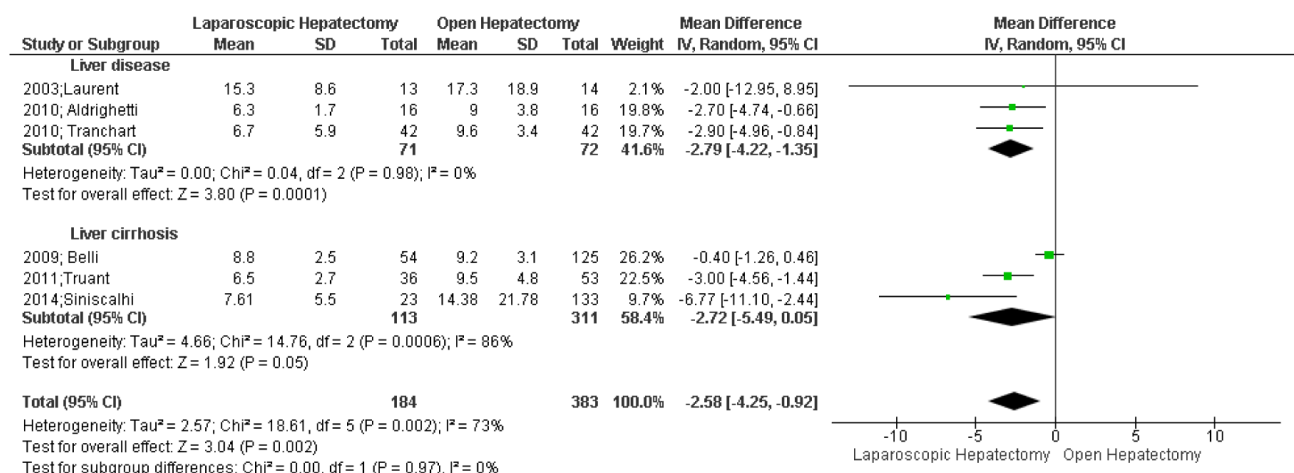
Figure 3. Forest plot depicting mean difference (MD) for hospital stay (days) in the included studies.

Table 1. Characteristics of the included studies (laparoscopic vs open liver resection)

Year; first author	Type of study	Country	Newcastle-Ottawa Scale	Inclusion criteria	LLR indications
2016; Sotiropoulos [15]	Retrospective not matched	Greece	*******	N/A	N/A
2015; Komatsu [16]	Retrospective matched pair 1:1	France	*******	Absence of extrahepatic metastasis; no history of previous hepatectomy; without spread to other organs, (diaphragm or Gerota's fascia); an adequate tumor margin, (no cases associated with tumor thrombus invasion into main or first branch the major hepatic or portal veins)	Tumor size alone or history of preoperative portal vein embolization (PVE) no contraindication
2010; Aldrighetti [17]	Retrospective matched 1:1	Italy	********	Child-Pugh class A; no previous upper major abdominal surgery; cardiac or respiratory impairments	Lesions in the left lobe or peripheral right segments of the liver (II-VI); tumors smaller than 12 cm; no doubts about adequate disease-free margins
2010; Tranchart [18]	Retrospective matched 1:1	France	******	N/A	Subcapsular lesions in the anterior or lateral segments (II- VI) (except for pedunculated ones); solitary tumors smaller than 5 cm; tumors treated by limited resection (<3 segments); Child-Pugh class A cirrhosis
2003; Laurent [19]	Prospective matched	France	******	HCC in chronic liver disease; solitary tumors; subcapsular lesions localized in the anterior or lateral segments of the liver i.e., II-VI (Couinaud's classification)	Lesions in the anterior or lateral segments (II-VI)

Liver cirrhosis (laparoscopic hepatectomy vs open hepatectomy)

Year; first author	Type of study	Country	Newcastle-Ottawa Scale	Inclusion criteria	LLR indications
2016; Sposito [20]	Retrospective matched 1:1	Italy	********	HCC in cirrhotic livers; no conversions to laparotomy before any attempt at resection was started	Lesions in the anterior or lateral segments (II–VI) 'favourable' for LLR; lesions in segments I, VII and VIII 'unfavourable' for LLR
2014; Siniscalhi [21]	Retrospective not matched	Italy	******	Minor resection (wedge resection, segmentectomy, bisegmentectomy, or left lobectomy); no conversions to laparotomy; lesion characteristics compatible with a laparoscopic approach	Lesions in the anterior segments (II- VI); small number of lesions (≤3); tumors smaller than 5 cm;
2014; Memeo [22]	Retrospective matched 1:1	France	*******	No history of upper abdominal surgery; histologically confirmed F4 cirrhosis (Metavir score)	N/A
2011; Truant [24]	Retrospective matched	France	*******	N/A	Subcapsular lesions in the anterior or lateral segments (II- VI) (except for pedunculated ones); solitary tumors smaller than 5 cm; tumors treated by limited resection (<3 segments); Child-Pugh class A cirrhosis
2009; Belli [23]	Retrospective not matched	Italy	*****	Child–Pugh class A/B low grade; no signs of severe portal hypertension (oesophageal varices <F29); platelet count of at least 80×109/l; no Child–Pugh class C or B high grade; no ASA>3	Exophytic or subcapsular lesions in the left segments (II, III, IVb) or peripheral right segments (V, VI); tumors smaller than 5 cm

N/A: not available

Table 2. Patient characteristics (laparoscopic vs open liver resection)

Year; first author	Patients, n	Sex (Males)	Age (Years)	Tumor size(cm) (the largest)	Convert to open	HBV	HCV	Liver cirrhosis	ASA	Anterior; Posterior
2016; Sotiropoulos [15]	11 vs 21	9 vs 20	65(54-81) vs 70(40-89)	4.7 (1.8-9.7) vs 6.1 (2.5-22)	0	7 vs 10	2	12	N/A	10 vs 10; 1 vs 11
2015; Komatsu [16]	38 vs 38	34 vs 33	61.5 (12.2) vs 61.7 (16.1)	4.7 (2.3-1.80) vs 8.5 (2.0–1.8)	13	N/A	7 vs 6	N/A	I:6 vs 7 II:21 vs 21 III:10 vs 5 IV: 0 vs 1 Unknown: 1 vs 4	N/A
2010; Aldrighetti [17]	16 vs 16	11 vs 12	65±10 vs 71±6	4±2.2 vs 4.6±2.5	1	N/A	N/A	9 vs 9	II: 14 vs 8 III: 2 vs 8	15 vs 11; 1 vs 4
2010; Tranchart [18]	42 vs 42	15 vs 14	63.7 ±13.1 vs 65.7 ± 7.1	3.58 ± 1.75 vs 3.68 ± 2.09	2	N/A	N/A	31 vs 34	I: 8 vs 7 II:22 vs 23 III:12 vs 12	N/A
2003; Laurent [19]	13 vs 14	10 vs 10	62.6 ±9.5 vs 65.9±5.5	3.35±0.89 vs 3.43±1.05	2	4 vs 6	5 vs 5	N/A	N/A	13 vs 14; 0 vs 0

Liver cirrhosis (laparoscopic hepatectomy vs open hepatectomy)

Year; first author	Patients, n	Sex (Males)	Age (Years)	Tumor size(cm) (the largest)	Convert to open	HBV	HCV	Liver cirrhosis	ASA	Anterior; Posterior
2016; Sposito [20]	43 vs 43	28 vs 35	66 (40–85) vs 68 (49–83)	2.6 (1.0–6.5) vs 2.2 (1.0–8.5) SS	2	6 (14) vs 10 (23)	28 (65) vs 23 (53)	43 vs 43	N/A	46 vs 43 9 vs 13 (number of resected nodules according to location)
2014; Siniscalhi [21]	23 vs 133	15 vs 104	57.91 ±10.92 vs 63.26±7.89	3.21 ±1.04 vs 3.6 ±1.64	N/A	6 vs 35	17 vs 88	23 vs 133	N/A	N/A
2014; Memeo [22]	45 vs 45	35 vs 37	62 (34–75) vs 60 (43–80)	3.2 (0.9–11) vs 3.7 (0.1–15)	N/A	16 vs 13	18 vs 17	45 vs 45	N/A	54 vs 44; 4 vs 15
2011; Truant [24]	36 vs 53	31/5 vs 47/6	60.6 ±10.2 vs 63.3 ± 7.6	2.9 ± 1.2 vs 3.1 ± 1.2	7	3 vs 4	4 vs 6	36 vs 53	>II 11 vs 14	N/A
2009; Belli [23]	54 vs 125	31 vs 78	63.3 ± 6.1 vs 61.5 ± 7.8	3.8 ± 1.3 vs 6.0 ±2.3	4	2 vs 16	50 vs 102	54 vs 125	I: 18 vs 44 II: 25 vs 56 III: 11 vs 25	N/A

N/A: not available

Table 3. Short and long term outcomes (laparoscopic vs open liver resection)

Year; first author	Operative time (min)	Estimated blood loss (ml): Blood transfusion	Length of stay (days)	Resection margin (cm):R0 resection	30-d mortality	Morbidity	1-OS: 3-OS: 5-OS	1-DFS: 3-DFS: 5-DFS	Recurrene rates
2016; Sotiropoulos [15]	120 (90-180) vs 200 (90-300)	N/A: 4 vs 19	5 (4-14) vs 8 (5-25)	N/A: 11 vs 18	0/11 vs 1/21	2 vs 9	11/11 vs 21/21: 9/11 vs 14/21: N/A	N/A N/A N/A	1/11 vs 8/21
2015; Komatsu [16]	365 (180–600) vs 300 (210–425)	100.0 (20–900) vs 80.0 (20–800): 2 vs 1	7.5 (3–51) vs 10.0 (5–53)	N/A: 6 (15.8) vs 6 (15.8)	N/A	12/38 vs 23/38	33/38 vs 33/38: 28/38 vs 26/38: N/A	22/38 vs 18/38: 19/38 vs 11/38: N/A	N/A
2010; Aldrighetti [17]	150±57 vs 240±121	258±186 vs 617±433: 4 vs 6	6.3±1.7 vs 9±3.8	0.11±0.8 vs 0.7±0.4: 16 vs 13	0/16 vs 0/16	4/16 vs 7/16	N/A: N/A: N/A	N/A: N/A: N/A	6/16 vs 6/16
2010; Tranchart [18]	233.1 ± 92.7 vs 221.8 ± 46.3	364.3 ± 435.7 vs 723.7 ± 559.5: 4(9.5) vs 7 (16.7)	6.7 ± 5.9 vs 9.6 ± 3.4	1.04 ± 0.8 vs 1.06 ± 0.9: N/A	1/36 vs 1/53	4/36 vs 5/53	39/36 vs 34/53: 31/36 vs 31/53: 25/36 vs 20/53	34/36 vs 30/53: 26/36 vs 23/53: 19/36 vs 16/53	10/36 vs 12/53
2003; Laurent [19]	267±79 vs 182±57	620±130 vs 720±240:1 vs 4	15.3±8.6 vs 17.3±18.9	0.9±0.25 vs 0.88±0.13: N/A	0/13 vs 2/14	4 vs 7	N/A: 12/13 vs 8/14: N/A	N/A: N/A: N/A	5/13 vs 7/14

Liver cirrhosis (laparoscopic hepatectomy vs open hepatectomy)

Year; first author	Operative time (min)	Estimated blood loss (ml): Blood transfusion	Length of stay (days)	Resection margin (cm):R0 resection	30-d mortality	Morbidity	1-OS: 3-OS: 5-OS	1-DFS: 3-DFS: 5-DFS	Recurrene rates
2016; Sposito [20]	199 (110–448) vs 199 (120–370)	N/A: N/A	5 (1–31) vs 8 (5–42)	6 (1–20) vs 5 (1–30): 42 (98) vs 42 (98)	0 vs 0	8 vs 21	N/A: 32/43 vs 34/43: 16/43 vs 20/43	N/A: 18/43 vs 19/43: 11/43 vs 5/43	N/A
2014; Siniscalhi [21]	175 ± 9 vs 165 ± 80	N/A 0/23 vs 36/133	7.61 ± 5.5 vs 14.38 ±21.78	N/A: 22 vs 129	0/23 vs 10/133	5/23 vs 47/133	N/A N/A N/A	N/A N/A N/A	N/A
2014; Memeo [22]	140 (45–360) vs 180 (90–360)	200 (0–1,500) vs 200 (0–2,000): 0 (0–4) vs 0 (0–10)	7 (0–69) vs 12 (0–34)	1 (0–5) vs 0.6 (0–5.8): N/A	0/45 vs 2/45 (4.5)	9/45 vs 20/45	40/45 vs 28/45: N/A: 27/45 vs 20/45	36/45 vs 27/45: N/A: 9/45 vs 10/45	25/45 vs 28/45
2011; Truant [24]	193.4 ± 104 vs 215.8 ± 88.7	452.2 ± 442 vs 447.2 ± 449.8: 1(2.8) vs 2 (3.8)	6.5 ± 2.7 vs 9.5 ± 4.8	0.95 ± 0.28 vs 0.86 ± 0.17: N/A	0/36 vs 4/53	9/36 vs 19/53	N/A N/A 13/36 vs 18/53	N/A	16/26 vs 23/53
2009; Belli [23]	167 ±36 vs 185 ± 61.3	297 ± 134 vs 580 ± 12: 6 (11) vs 32 (25.6)	8.4 ± 2.5 vs 9.2 ± 3.1	N/A: 54 vs 117	1/54 vs 5/125	10/54 vs 45/125	51/54 vs 107/125: 36/54 vs 75/125: N/A	42/54 vs 98/125: 28/54 vs 73/125: N/A	N/A

N/A: not available

went LLR and OLR (268 patients, MD -154.27ml, 95% CI -434.91, 126.37, p=0.28, Figure 2). Neither R0 resection margin nor resection margin width was found significantly different among the two groups (561 patients, OR 1.95, 95% CI 0.87, 4.36, p=0.11, and 232 patients, MD -0.04cm, 95% CI 0.22, 0.15, p=0.70, respectively). The same was also reflected in the case of subgroup analysis. Interestingly, mean tumor size did not differ in studies involving patients from the two groups (567 patients, MD -0.61 cm, 95% CI -1.39, 0.17, p=0.13).

Postoperative outcomes revealed a significantly prolonged hospital stay for patients in the open group when compared with those in the lapa-

roscopic group (567 patients, MD -2.58 days, 95% CI 4.25, -0.92, p=0.002, Figure 3). Furthermore, significantly increased morbidity rates were also detected among patients operated through open approach in comparison with those who underwent LLR (851 patients, OR 0.38, 95% CI 0.27, 0.53 p<0.00001, Figure 4). Moreover, 30-day postoperative mortality rates were improved in patients who were laparoscopically operated when compared to those who underwent OLR for HCC (775 patients, OR 0.31, 95% CI 0.11, 0.88, p=0.03, Figure 5). Concerning subgroup analysis, in the cirrhotic subgroup, mortality rates reached statistical significance in favor of patients undergoing LLR who
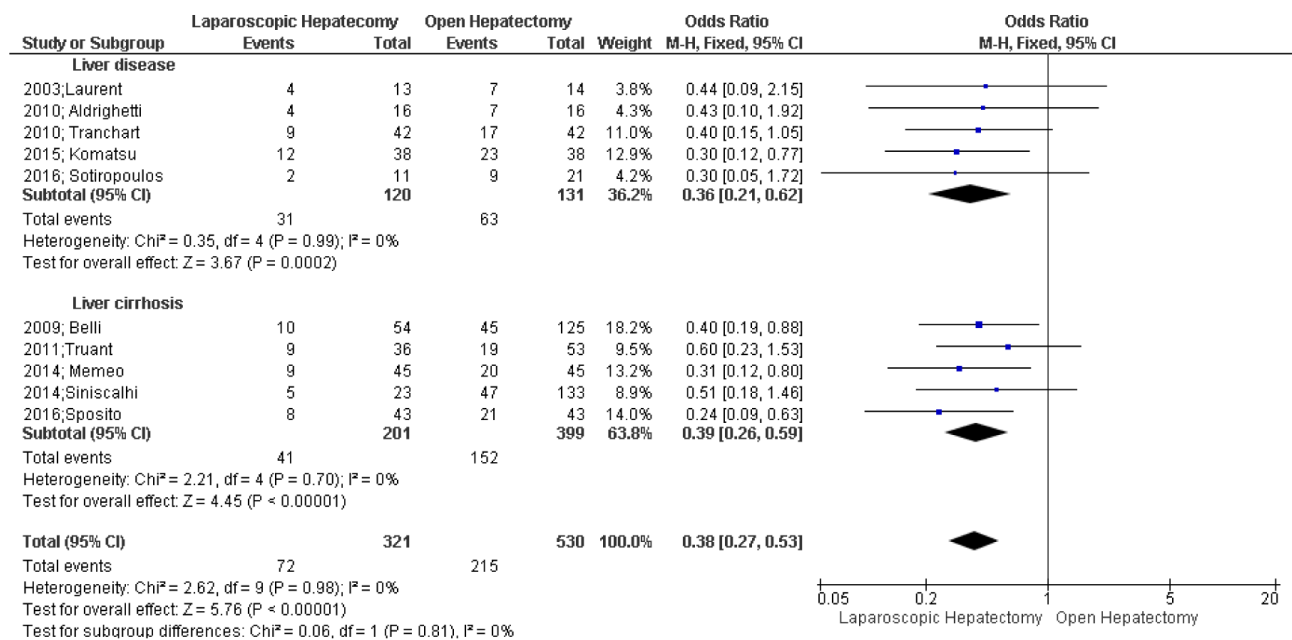

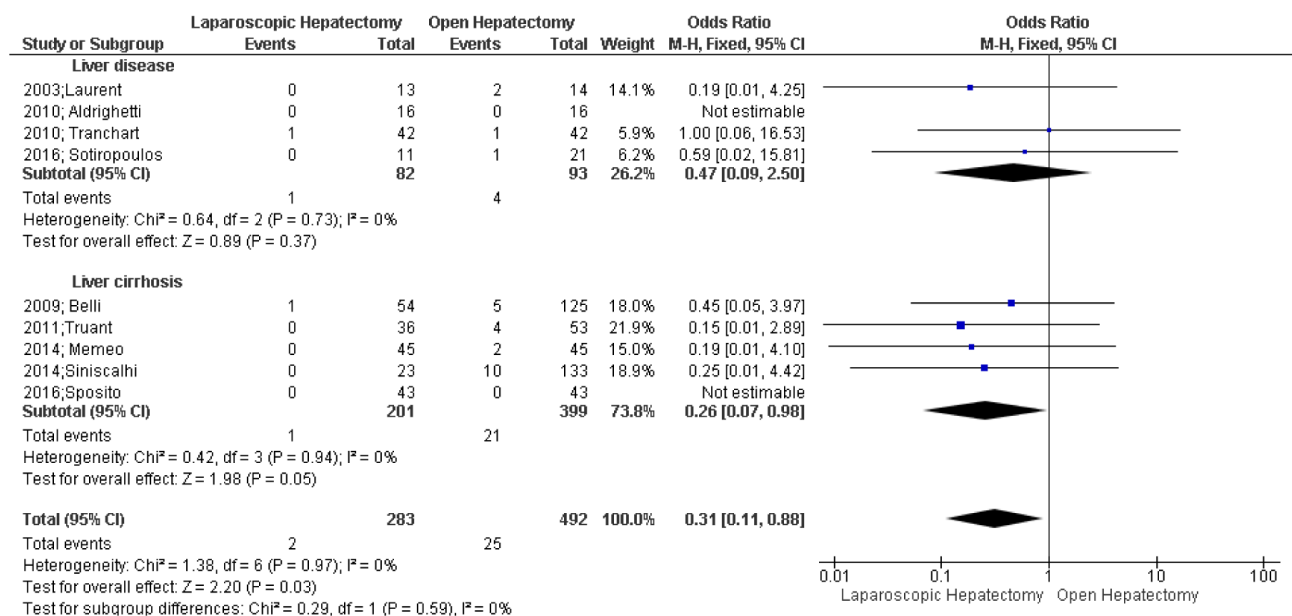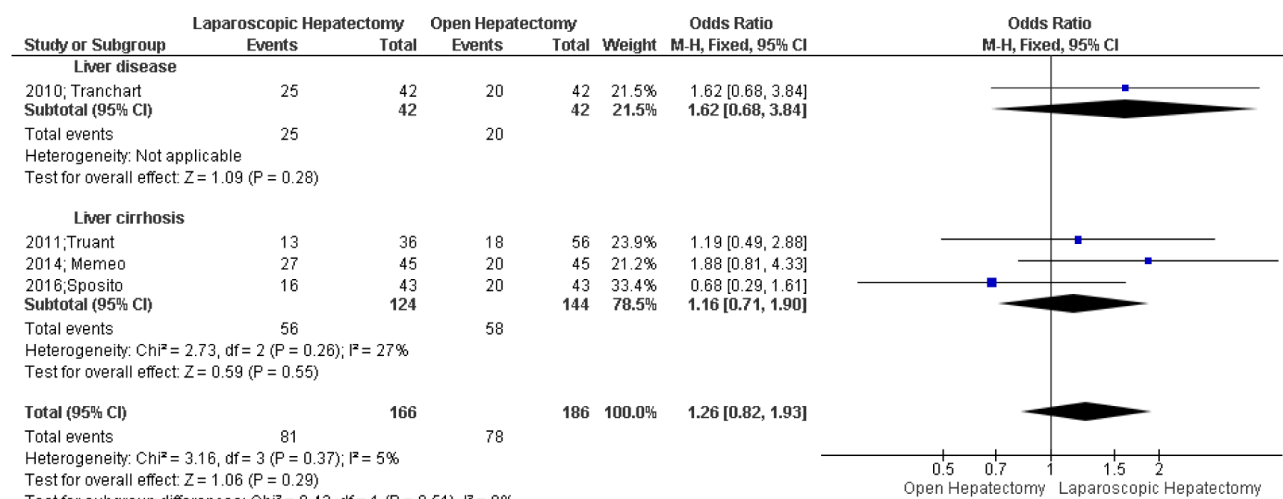**Figure 4.** Forest plot depicting odds ratio (OR) for morbidity in the included studies.

Figure 5. Forest plot depicting odds ratio (OR) for 30-day mortality in the included studies.

displayed decreased mortality rates, whereas in the non-cirrhotic subgroup mortality did not differ between the two groups (600 patients, OR 0.26, 95% CI 0.07, 0.98, p=0.05, and 175 patients, OR 0.47, 95% CI 0.09, 2.50, p=0.37, respectively) (Figure 5).

One-year OS rates were found superior for patients in the LLR group when compared with those in the OLR group (292 patients, OR 2.12, 95% CI 1.17, 3.87, p=0.01). Interestingly, statistical significance was not documented when comparing patients in the non-cirrhotic subgroup (202 patients, OR 1.42, 95% CI 0.68, 2.96, p=0.35), whereas when comparing the patients in the cirrhotic subgroup, outcomes differed significantly (68 patients, OR 4.86, 95% CI 1.60, 14.71, p=0.005). However, 3-year OS as well as 5-year OS presented not statistical significant differences among the two groups (297 patients, OR 1.20, 95% CI 0.71, 2.04, p=0.49 and 352 patients, OR 1.26, 95% CI 0.82, 1.93, p=0.29, Figure 6, respectively). A similar result was also reflected in the case of subgroup analysis. Neither

1-year DFS nor 3-year DFS differed among the study group and the controls (429 patients, OR 1.52, 95% CI 0.97, 2.37, p=0.07 and 425 patients, OR 1.11, 95% CI 0.75, 1.65 p=0.61, respectively). Five-year DFS was found improved among patients in the laparoscopic group (349 patients, OR 1.70, 95% CI 1.05, 2.72, p=0.03) (Figure 7). This was also observed in the case of the cirrhotic subgroup whereas in the non-cirrhotic subgroup the results were not different (265 patients, OR 1.87, 95% CI 1.06, 3.30, p=0.03 and 35 patients, OR 1.34, 95% CI 0.56, 3.20, p=0.51, data from one study, respectively) (Figure 7). Finally, tumor recurrence analysis did not present any differences between the two groups (354 patients, OR 0.77, 95% CI 0.49, 1.20, p=0.25).

Among the studied parameters 5 were found to present heterogeneity. In particular, the study of Belli et al. [23] led to heterogeneity of the studies in the analysis of length of hospital stay. Heterogeneity: $Tau^2=2.57$; $x^2=18.61$, df=5 (p=0.002); $I^2=73\%$

Figure 6. Forest plot depicting odds ratio (OR) for 5-year overall survival in the included studies.
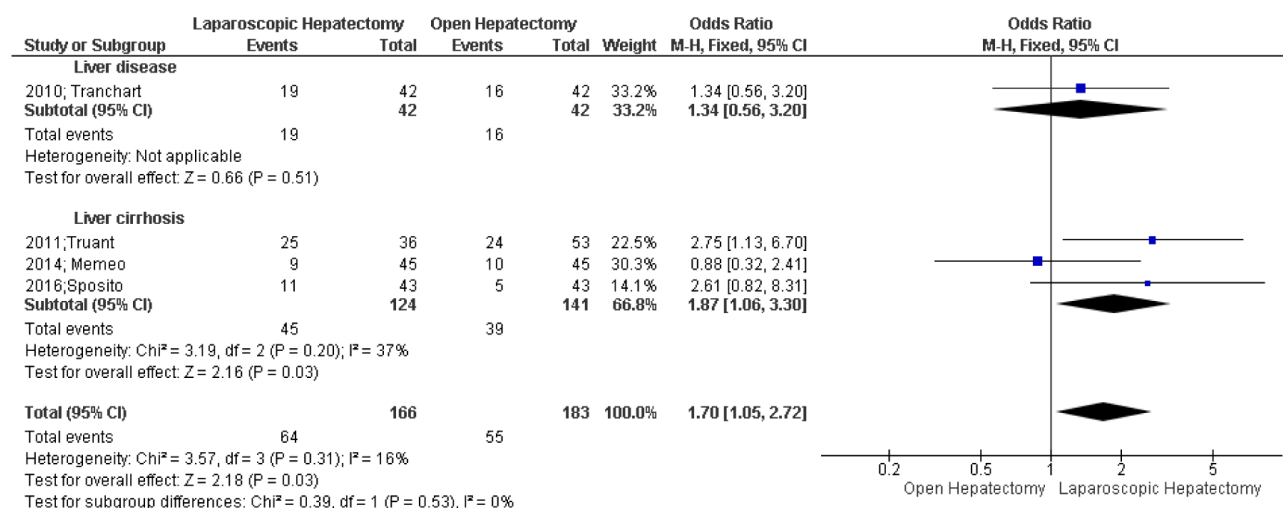
Figure 7. Forest plot depicting odds ratio (OR) for 5-year disease free survival in the included studies.

when included, and Heterogeneity: $Tau^2=0.00$; $x^2=3.00$, df=4 (p=0.56); $I^2=0\%$ when excluded. In the analysis of blood loss the study of Truant et al. [24] detected heterogeneity: Heterogeneity: $Tau^2=13758.13$; $x^2=15.01$, df=4 (p=0.005); $I^2=73\%$ when included, and Heterogeneity: $Tau^2=6318.20$; $x^2=6.90$, df=3 (p=0.08); $I^2=57\%$ when excluded. In the case of operative time the study of Laurent et al. [19] also detected heterogeneity: Heterogeneity of: $Tau^2=1035.98$; $x^2=22.36$, df=5 (p=0.0004); $I^2=78\%$ when included, and Heterogeneity: $Tau^2=348.28$; $x^2=9.15$, df=4 (p=0.06); $I^2=56\%$ when excluded. The study by Belli et al. [23] was responsible for heterogeneity in the case of tumor size; when it was included heterogeneity was: $Tau^2=0.79$; $x^2=40.51$, df=5 (p<0.00001); $I^2=88\%$ and when excluded heterogeneity was: $Tau^2=0.00$; $x^2=0.84$, df=4 (p=0.93); $I^2=0\%$. Finally, in case of resection margin the study of Aldrighetti et al. [17] showed heterogeneity: Heterogeneity: $Tau^2=0.02$; $x^2=9.03$, df=5 (p=0.03); $I^2=67\%$ when included, and Heterogeneity: $Tau^2=0.00$; $x^2=0.77$, df=2 (p=0.068); $I^2=0\%$ when excluded. Funnel plots presented no significant publication bias.

Discussion

Laparoscopic liver resections were initially reported in the early 1990s but unlike other laparoscopic procedures their establishment as safe procedures with acceptable morbidity, mortality and long-term oncologic outcomes was delayed. Initial controversy between enthusiasm and reluctance on the performance of such procedures led to the organization of the 1st World Consensus Meeting on Laparoscopic Hepatectomy (LH) in 2008. The international position on laparoscopic liver surgery stated that it is a safe and effective approach to the surgical management of liver disease in the hands of trained surgeons with experience in hepatobiliary and laparoscopic surgery [25].

Treatment options for cirrhotic patients with HCC, which constitute a particularly high-risk patient group, can often be limited due to underlying severe chronic liver disease. Liver transplantation represents a potentially curative treatment for HCC in patients with liver cirrhosis; nevertheless application on a large scale is not feasible due to various negative factors such as patient age, alcohol abuse, associated diseases, and donor shortages [26]. Undeniably, underlying cirrhosis is a major risk factor for liver resections. Open liver surgery is compatible with large incisions, requires major mobilizations as well as hepatic resection. Such manipulations in this high-risk group can potentially engender intraoperative risks such as

bleeding or may secondarily lead to development of intractable ascites in the early postoperative course of the patient [27]. An additional postoperative higher complication rate associated with open liver resections can result in elongation of the patient's hospital stay.

Statistically significant results

Blood loss during hepatic resections constitutes a major concern especially in the setting of chronic liver disease and has been associated with unfavorable short- and long-term postoperative results. Evolution in laparoscopic techniques and equipment in combination with the effect of pneumoperitoneum on hepatic veins' hemostasis play an important role in decreasing blood loss during laparoscopic resections [22]. Blood loss was found significantly higher in the ORL group as also documented in other several meta-analyses [28-35]. Nevertheless such a result could be attributed to more complicated resections most commonly performed through the open approach. Although blood loss between cirrhotic patients operated by laparoscopy and those operated through open approach did not differ, the overall comparison favored the laparoscopic approach (Figure 2). Comparison between groups concerning need for transfusion consistently favored the laparoscopic approach similarly to previous analyses [28-31,34,35].

Hospital stay was found significantly protracted in the ORL group, highly possibly related to the importantly lower complication rates demonstrated in LLR group (Figure 3). The laparoscopic approach permits avoidance of large incisions; therefore decreasing pain and the need for analgesics in the postoperative setting it allows early ambulation, faster resume of oral intake and faster discharge. Avoiding large abdominal wall incisions also has a major role in the decreased complications' rate; preservation of collateral veins omits occurrence of ascites, a major risk factor especially for cirrhotic patients [23]. Thirty-day postoperative mortality and morbidity were significantly higher in the open approach group, confirming the results of 6 previous meta-analyses (Figure 4) [29-32,34,36]. One-year OS as well as 5-year DFS were higher in the LLR group. Studies demonstrating an association between blood loss and disease-free intervals after HCC resection have previously been published [37,38]

Statistically non-significant results

Operative time was not different between the groups. Although initially laparoscopic resections

were more time consuming, evolution in parenchyma-transecting devices along with laparoscopic proficiency have resulted in shorter resection times. Of note, the majority of resections described in the included studies were anterior (Table 2) and some would argue that resections in posterior segments could be more time consuming with laparoscopy as it was also supported by a study evaluating LLRs in posterior vs anterior segments [39]. Laparoscopic resection in cirrhotic patients was longer than with the open approach, yet such result is anticipated, as transection of hepatic parenchyma needs to proceed with caution due to the fear of bleeding. A recent study reported no difference in operative time between cirrhotic and non-cirrhotic patients with HCC located in posterior segments [40]. Similarly, non-significant difference in operative time was shown in previous studies [28-31,33-35]. Fear of oncologically inadequate margin was a major obstacle for laparoscopic resection in its early steps; inability to palpate lesions as in the open approach was overcome by the performance of endoscopic ultrasonography, enabling hepatobiliary surgeons to accurately assess the optimal resection margin. Resection margins as well as R0 resection rates were also not different among the groups. Interestingly, tumor size was also not different, underlining the efficacy of the laparoscopic approach. However, such result must be interpreted with caution; in the majority of the included studies, laparoscopic resections were performed in tumors predominantly located in anterior segments (II-VI) respecting the recommendations of the Louisville statement [24], and were therefore more easily accessible. Three-year and 5-year OS as well as 1-year and 3-year DFS were not different among the groups as was also indicated in previous meta-analyses [27-29].

Strengths and weaknesses

Our study compared the results of laparoscopic with open approach from 10 studies conducted in Europe, evaluating the short and long-term outcomes of patients undergoing liver resection for HCC. The present meta-analysis, apart from the overall comparison between the laparoscopic and the open technique, also included additional comparisons for cirrhotic and non-cirrhotic patients. This supplementary subgroup analysis allows for additional evaluation of the influence of underlying chronic liver disease on the outcomes. Our meta-analysis assessed the largest number of short and long-term parameters of patients operated for HCC either by laparoscopy or laparotomy. It presented quality assessment of the included studies, which provided a comparatively high mean and median score with a minor standard deviation and a small difference between the minimum and the maximum score, stating these studies as reliable as well as methodologically adequate without great variances among them in terms of quality. To our knowledge, this is the only meta-analysis assessing European studies analyzing the short- and long-term results of LLR vs OLR for HCC. On the contrary, our results may be subjected to potential bias, including selection bias, selective reporting and attrition bias due to significant heterogeneity among the different studies regarding several parameters, as presented in Table 1. Consequently, there is a high risk of bias despite the fact that the funnel plots seemed to be symmetrical. All the studies that were included were non-randomized retrospective studies with or without matching. Selection of patients for each group was based on subjective criteria, such as surgeon's experience and evaluation, patient's potential preference and tumor characteristics. This, however, was not the case for all studies, because a matched analysis was performed according to main patient characteristics in many cases. The small number of included patients in the majority of the studies constitutes another limitation of our meta-analysis. Furthermore, in the case of continuous parameters, outcomes were cited in different ways and as a result some of them were excluded from the analysis. Finally, the decision to include articles written in English could probably be considered as a bias. Nonetheless, during the searching process no non-English studies were identified.

The present meta-analysis demonstrates the superiority of laparoscopic over open approach for same size tumors. Nevertheless, the present outcomes must be interpreted with caution as the majority of the included studies reported results from LLR on lesions located in anterior segments. Surgeons performing laparoscopic resections must always conform to the international recommendations while location and stage of tumor continue to play a cardinal role in the selection of the approach. Cirrhotic patients benefit from laparoscopy in terms of shorter hospital stay, complication rate and long-term oncologic outcomes.

Conflict of interests

The authors declare no confict of interests.

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