Article

Oncological Outcomes after Laparoscopic and Open Liver Resection in patients with Colorectal Liver Metastases: A Single Centre Propensity Score Matched Study

A Diaz-Garcia, R Young, T Gilbert, A Rehman, A Gordon-Weeks, S Fenwick, H Malik, R Jones and R Diaz-Nieto*

Liverpool University Hospital, UK

* Correspondence: rafael.diaz-nieto@liverpoolft.nhs.uk

Abstract: Introduction Minimally invasive approaches to oncological liver resection is common in many hepatobiliary centres. This study aims to compare the key oncological and survival outcomes of patients with colorectal liver metastases (CRLM) undergoing laparoscopic or open resections using propensity score matching (PSM). Methods: A single-centre retrospective study was performed using a prospective database of patients undergoing liver resection for CRLM between January 2016 and December 2019. Different co-variates were selected for matching using PSM. Pre-matching and post-matching analyses were compared. Surgical and survival outcomes were analysed. Results: In total, 303 patients who met the inclusion criteria were identified: 214 underwent open liver resection (OLR) and 91 laparoscopic liver resection (LLR). LLR had a significantly reduced length of intensive treatment unit (ITU) and overall in-patient stay but longer pringle and operative times. In the unmatched cohort, the median overall and disease-free survival time was significantly longer in patients undergoing laparoscopic compared with open surgery. A PSM model demonstrated significantly reduced blood loss and length of hospital stay, with a significantly greater Pringle and operative time in the LLR group. Differences seen in overall and disease-free survival were lost with propensity score matching, possibly due to lack of bi-lobar disease within the minimally invasive group. Conclusion: In selected patients with CRLM, LLR presents similar survival and oncological outcomes with the advantages of the short-term results associated with the laparoscopic approach.

Keywords: liver surgery; colorectal cancer; laparoscopy; survival

1. Introduction

The GLOBOCAN 2020 study (1) estimates that colorectal cancer is the third most common cancer globally, making up 10% of total cases in the world, whilst being the second most common cause of cancer death in both males and females (9.4% of all cancer deaths).

Due to characteristics of colorectal cancer, the most common non-nodal site of metastatic tumour spread in these patients is the liver. At time of diagnosis, 15-20% of patients may present with synchronous colorectal liver metastases (CRLM) and up to 25% of patients develop metachronous CRLM (2). At the initial time of diagnosis, approximately 20% of patients with liver metastases are resectable (2). While a high proportion of patients present with initially unresectable CRLM, advances in chemotherapy and the advent of targeted therapies have enabled initially non-resectable disease to become resectable with a subsequently improved prognosis. However, despite the improvements and advances in the different therapeutic modalities, liver resection is the only potential curative treatment providing long-term survival, with 5- and 10-year overall survival (OS) rates being 33%–58% and 23%–39%, respectively (3-5).

Since the benefit in survival outcomes of CRLM surgery was established, the operative approach to CRC metastases has traditionally been open liver resection (OLR). However, since the introduction of laparoscopic liver resection (LLR) in the early 1990s (6-7), improvements in surgical devices and

 doi:10.20944/preprints202305.1737.v1

minimally invasive techniques have led to an increasingly common laparoscopy approach in the operative management of benign and malignant liver lesions, including CRLM (8). During the past decade a large number of studies have reported on the safety, feasibility, and oncological efficacy of the LLR in the management of primary and secondary liver lesions (9-10). Studies have highlighted the benefits of LLRs compared with conventional OLR, including less intraoperative blood loss, decreased postoperative pain, lower postoperative morbidity rates, shorter postoperative length of hospital stay and earlier return to functional activities (11-14).

Although some studies have reported superior oncological results with the laparoscopic approach (15), these results have to be interpreted with caution owing to the potential role of selection bias and its effect on outcomes. Evidence on laparoscopic approach to CRLM resection is most commonly based on retrospective analyses of case-matched studies or meta-analyses of non-randomized studies. To date, only one randomized controlled study (OSLO-COMET) has been conducted showing benefits for minimal-invasive hepatectomies (MIH) in CRLM resection (16).

The propensity-score matching (PSM) analysis has gained popularity in recent years as a statistical method to adjust for known confounding factors and thus reduce the impact of selection bias in retrospective studies (17,18). For that reason, PSM has been often used for the comparison of surgical techniques, to create comparable treatment groups. The aim of this study was to evaluate and compare surgical outcomes of overall survival and disease-free survival in OLR and LLR, with and without using a PSM.

2. Methods

Patients undergoing resection of colorectal liver metastasis between January 2016 and December 2019 at the Aintree University Hospital NHS Trust (Liverpool) were identified by review of a prospectively-maintained database. All patients underwent pre-operative computed tomography (CT) chest/abdomen/pelvis, magnetic resonance imaging (MRI) liver and fluorodeoxyglucose - positron emission tomography (FDG-PET) scan discussed at the multidisciplinary team meeting. Patients received 6-monthly CT chest/abdomen/pelvis for the first two years following surgery and yearly thereafter for 5 years.

Overall survival is defined as the time between surgery and death or censoring and liver-specific and disease-free survival are defined as the time between surgery and hepatic or any recurrence, as documented on cross-sectional imaging.

Age, body mass index (BMI), neoadjuvant chemotherapy, synchronicity and side of primary (right colon versus left or rectum), colonic nodal disease, synchronous lung metastases, major resection number and size of largest metastasis were considered possible confounders of the association between operative approach and outcomes. Differences between baseline confounders were assessed using chi-squared tests for categorical variables. Normality of continuous variables was assessed using Shapiro-Wilks tests. Median and inter-quartile range were reported for skewed continuous confounders and differences were compared using Wilcoxon Rank tests.

The association between type of surgery and each outcome was first assessed in an unadjusted analysis. Survival analysis methods were used to assess time-to-event outcomes. Kaplan-Meier curves were used to visually inspect difference in recurrence free survival, and Log-rank tests to statistically assess differences. Cox-proportional hazards models were used to assess the association between surgery type and risk of recurrence. Logistic regression was used to assess the binary margin outcome.

Since the association between surgery type and surgery outcome may have been confounded by a number of baseline covariates, we first adjusted for these covariates in a regression model for each outcome. We then used PSM to further investigate potential confounding and particularly the contribution of selection bias to differences in outcome between the laparoscopic and open approaches. Propensity scores were generated using a logistic regression model including surgery type as the outcome and the full list of possible confounders as explanatory variables. The propensity scores were used in two ways. Firstly, we performed PSM using a nearest-neighbour method and a

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 May 2023 doi:10.20944/preprints202305.1737.v1

caliper of 0.25. Propensity score matches for each laparoscopic case were selected without replacement, and each regression model was estimated on the propensity matched dataset.

3. Results

We identified 303 patients who met the inclusion criteria, of whom 214 underwent hepatectomy by the open approach and 91 laparoscopically. Demographic, operative and outcome details of these patients are demonstrated in **Table 1**. Patients who underwent laparoscopic surgery were significantly less likely to have bi-lobar liver metastasis and when compared with the open approach, had a significantly smaller number of metastases. Laparoscopic patients had a significantly longer operation and Pringle time but less blood loss and a significantly reduced length of ITU and overall in-patient stay. The median overall and disease-free survival time was significantly longer in patients undergoing laparoscopic compared with open surgery (**fig. 1**). Comparing margin status, although there was no difference in absolute R1 status, laparoscopic surgery provided a significantly greater distance between tumour and resection edge.

Given the evident selection bias with regards operative approach, as demonstrated by the significantly reduced burden of disease demonstrated in patients undergoing laparoscopic surgery, we performed PSM to balance the cohorts based on pre-operative and biological variables (see methods for co-variate selection). This resulted in two cohorts, each containing 82 patients which demonstrated good matching (**Table 2**).

The PSM model demonstrated a significantly greater Pringle and operative time in the laparoscopic group in addition to significantly reduced blood loss and length of hospital stay (**Table 2**). However, after PSM there was no significant difference in either overall or disease-free survival between the laparoscopic or open approaches (**Fig. 2, Table 3**).

Table 1. Demographics of laparoscopic and open hepatectomy patients. *median (IQR), $mean (±SD), major hepatectomy defined as >3 liver segments, + includes any hepatic or extrahepatic metastasis.

	Open	**Laparoscopic**	***P***
N (%)	212	91	
Demographics			
Age (years)*	66 (57-72)	69 (61.5-74)	0.054
Sex (male)	134 (63.2)	54 (59.3)	0.891
BMI (kg/m^2)*	27.1 (24.1-30.4)	26.1 (23.4-29.4)	0.054
American Society of Anesthesiologists (ASA) scale 1 2 3 4	 15 (7.1) 146 (68.9) 50 (23.6) 1 (0.5)	 9 (9.9) 69 (75.8) 13 (14.3) 0 (0.0)	0.246
Anaerobic threshold$ (ml/min/kg)	11.5 (±3.3)	12.0 (±2.7)	0.283
Hemoglobin (Hb)$ (g/L)	134 (±15.3)	134 (±15.4)	0.848
White Cell Count (WCC)$ (10^9/L)	7.39 (±5.05)	6.95 (±1.73)	0.415
Tumour biology			
Carcinoembryonic antigen (CEA)* (ng/mL)	5.4 (2.4-18.7)	5.3 (2.4-14.4)	0.094
Neoadjuvant chemotherapy	134 (63.2)	46 (50.5)	0.054
Synchronous primary	121 (57.1)	49 (53.8)	0.694
Right-sided primary	157 (74.1)	69 (75.8)	0.857
Node positive primary	133 (62.7)	53 (58.2)	0.543
Synchronous lung metastasis	36 (17.0)	10 (11.0)	0.247
Bilobar liver metastasis	98 (46.2)	24 (26.4)	***0.002***
Number of metastases*	2 (1-4)	1 (1-3)	***0.002***
Largest metastasis (mm)*	30 (20-50)	30 (20-40)	0.579
Major hepatectomy	91 (42.9)	30 (33.0)	0.135
Outcomes			
Pringle time (min) *	25 (7-43)	37 (9-55)	***0.042***

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 May 2023 doi:10.20944/preprints202305.1737.v1

Highest intra-operative lactate*	2.3 (1.5-3.3)	2.5 (1.5-3.5)	0.511
Intraoperative blood loss (ml) *	450 (200-920)	300 (100-500)	***0.002***
Operation time (min) *	190 (150-270)	240 (180-300)	***0.002***
ITU stay (days) *	1 (0-2)	1 (0-1)	0.091
Hospital stay (days) *	6 (5-9)	5 (3-6)	***0.0008***
Complication >grade II	30 (14.2)	9 (9.9)	0.354
R1 (any metastasis+)	76 (35.9)	22 (24.2)	0.060
Closest margin (mm) *	2 (0.2-6)	5 (1-10)	***0.002***
30-day mortality	2 (0.94)	0 (0)	1.0
Median overall survival (months)	35	Undefined	***0.004***
Median disease-free survival (months)	9	18	***0.0003***

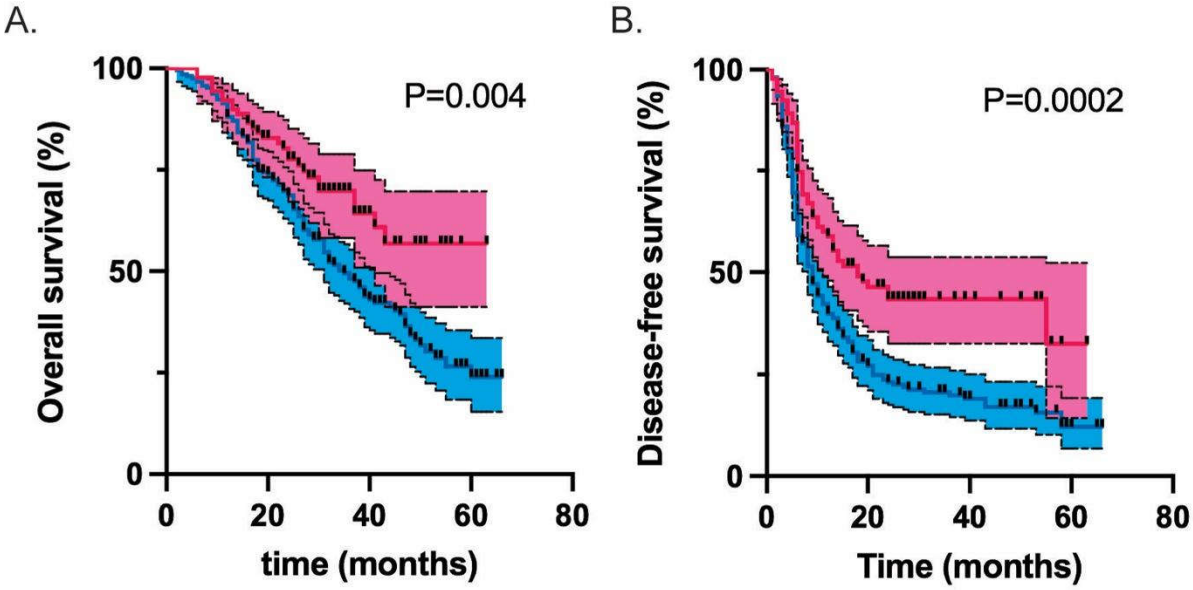

Figure 1. Overall (A) and Disease-free (B) survival curves in the unmatched cohorts demonstrating laparoscopic (red) and open (blue) approaches. Pink and blue shaded areas represent 95% confidence intervals respectively.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 May 2023 doi:10.20944/preprints202305.1737.v1

Table 2. Demographics and outcomes of propensity score-matched laparoscopic and open hepatectomy patients. *median (IQR), $mean (±SD), major hepatectomy defined as >3 liver segments, + includes any hepatic or extrahepatic metastasis.

	Open	Laparoscopic	*P*
Total N (%)	82 (50.0)	82 (50.0)	
Demographics			
Age (years)*	68 (61-75)	69 (59-74)	0.856
Sex (male)	48 (58.5)	51 (62.2)	
BMI (kg/m^2)*	25.9 (23.5-28.7)	26.5 (24.0-29.8)	0.302
ASA 1 2 3	 9 (11.0) 58 (70.7) 15 (18.3)	 9 (11.0) 60 (73.2) 13 (15.9)	 0.915
Anaerobic threshold$ (ml/min/kg)	12.0 (±2.9)	11.8 (±2.8)	0.680
Hb$ (g/L)	133 (±15.1)	133 (±15.9)	0.994
WCC$ (10^9/L)	6.82 (±1.6)	6.86 (±1.13)	0.907
Tumour biology			
CEA* (ng/mL)	5.5 (2.8-17.8)	5.0 (2.3-14.1)	0.269
Neoadjuvant chemotherapy	49 (59.8)	44 (53.7)	0.528
Synchronous primary	51 (62.2)	43 (52.4)	0.269
Right-sided primary	61 (74.4)	62 (75.6)	1.0
Node positive primary	55 (67.1)	48 (58.5)	0.332
Synchronous lung metastases	13 (15.9)	10 (12.2)	0.653
Bilobar metastases	30 (36.6)	24 (29.3)	0.406
Number of metastases*	2 (1-3)	1 (1-3)	0.492
Largest metastasis (mm)*	30 (20-45)	30 (22-41.5)	0.789
Major hepatectomy	28 (34.1)	29 (35.4)	1.0
Outcomes			
Pringle time (min) *	21.5 (2.0-40.5)	40 (12-55.5)	***0.005***
Highest intra-operative lactate*	2.23 (1.6-3.1)	2.5 (1.5-3.5)	0.499
Intraoperative blood loss (ml) *	400 (150-738)	300 (100-500)	***0.026***
Operation time (min) *	160 (120-240)	240 (180-300)	***<0.0001***
ITU stay (days) *	1 (0-2)	1 (0-1)	0.912
Hospital stay (days) *	6 (5-8)	5 (3-6)	***0.014***
Complication >grade II	6 (7.3)	7 (8.5)	1.0
R1 (any metastasis+)	29 (35.4)	21 (25.6)	0.235
Closest margin (mm) *	2 (0-6)	5 (1-10)	***0.008***
30-day mortality	1 (1.2)	0 (0)	1.0
Median overall survival (months)	50	undefined	0.442
Median disease-free survival (months)	12	15	0.096

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 25 May 2023 doi:10.20944/preprints202305.1737.v1

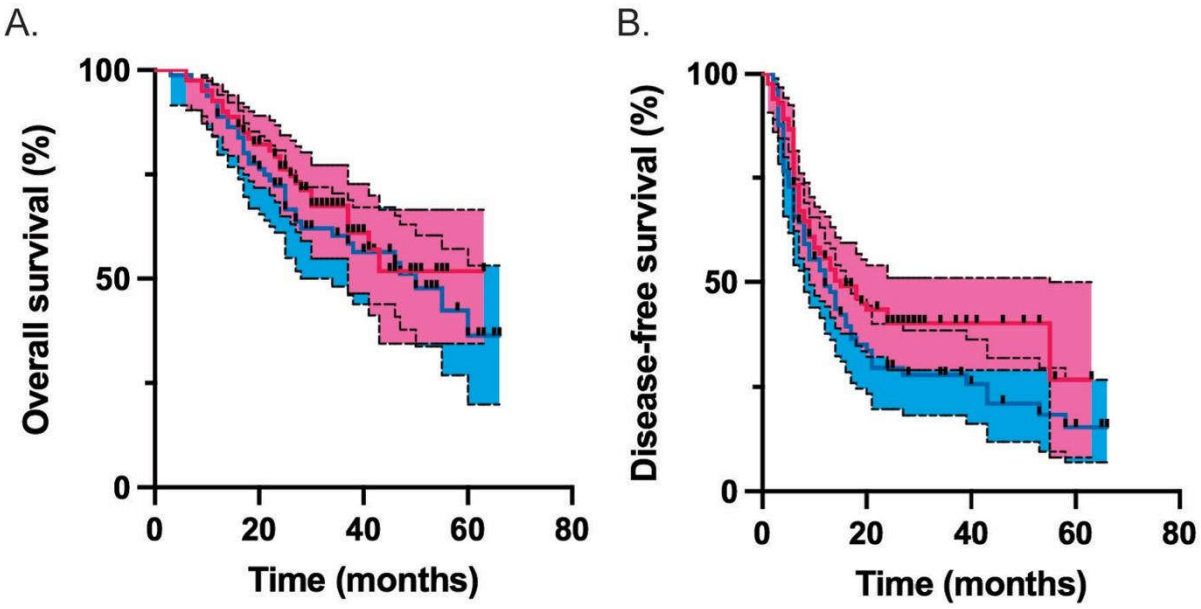

Figure 2. Overall (A) and Disease-free (B) survival curves in the PSM cohorts demonstrating laparoscopic (red) and open (blue) approaches. Pink and blue shaded areas represent 95% confidence intervals respectively. .

Table 3. Comparison of overall and disease-free survival represented at hazard ratios and 95% confidence intervals in the laparoscopic and open cohorts in the unadjusted and PSM cohorts.

	Overall survival		Disease-free survival	
Model	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Unadjusted	0.59 (0.42-0.85)	0.004	0.55 (0.41-0.76)	<0.001
Propensity score matched	0.83 (0.51-1.36)	0.442	0.74 (0.5-1.09)	0.129

4. Discussion

In recent years the laparoscopic approach for benign and malignant liver tumours has been increasing in frequency and complexity (major hepatectomies or one-stage surgery for CRLM). On the whole, the uptake of minimally invasive approaches in hepatobiliary surgery has been more gradual when compared to other operative subspecialties, primarily due to complexity of procedures and anatomy, difficulties with potential uncontrolled haemorrhage, and psychologically demanding learning curves (19). Currently, CRLM are the most common indication for laparoscopic liver resection in the Western world (20).

The present study reports a single institution's experience with patients diagnosed of CRLM, treated during a 3-year time period, before and after applying the PSM method. PSM analysis has been introduced aiming to overcome treatment or selection bias in retrospective studies by assembling patient cohorts with minimal differences in clinicopathological features allowing for a meaningful comparison (17, 18). In our study, we observed that those patients who underwent LLR were statistically less likely to have bilobar liver metastasis (46.2% vs 26.4%, p=0.002) and a significantly smaller number of liver metastases (2 vs 1, p=0.002) when compared with the OLR, in a manner similar to other studies (21-23).

Previous series from the literature (10,21-25) have highlighted the benefits of LLR for CRLM in terms of less intraoperative blood loss, lower morbidity rates, shorter postoperative length of hospital stay and superiority in functional recovery compared with OLR. Most of these reports were case

 doi:10.20944/preprints202305.1737.v1

series, case–control studies or meta-analyses of non-randomized studies (10, 21-27), and results have therefore been evaluated with caution due to the lack of randomized controlled trials (RCTs). So far, there are only a few RCTs that have been completed evaluating MIH for CRLM, the OSLO-COMET (16) and LapOpHuva (28), while another (ORANGE II Trial) had to be stopped prematurely owing to poor recruitment (29).

Regarding the benefits of LLR for CRLM, our analysis shows similar results to other studies. Operation time, intraoperative blood loss and Pringle time show statistically significant differences between the LLR and OLR groups, in agreement with Cipriani et. al (21) and Ratti et. al (24). Concerns regarding intraoperative haemorrhage could explain why the Pringle time is longer in the LLR group and this, combined with increased pneumoperitoneum pressures during LLR could lead to reduced operative blood loss.

In most surgical subspecialties, laparoscopy has been associated with decreased postoperative morbidity and mortality (30). Although there are no significant differences in our study in terms of complications and mortality, the postoperative ITU and hospital stay was significantly shorter after laparoscopic surgery, similar to other studies (11-14).

During the initial uptake of laparoscopic approaches in hepatobiliary surgery, early concerns were raised around ability to achieve robust oncological outcomes. However, well-designed randomized controlled trials (16,28) and meta-analyses (27) have shown its noninferiority to open surgery. In the present series, LLR appeared to be effective in terms of oncologic outcomes. Laparoscopic surgery provided a significantly greater distance between tumour and resection edge in comparison with open surgery (5mm vs 2mm, respectively). However, comparing margin status there was no significant difference in R1 status with or without PSM. The median overall survival (OS) and disease-free survival (DFS) show no significant differences between LLR and OLR groups with PSM.

Once different studies have determined the validity of the LLR for CRLM in terms of oncological outcomes, it cannot be ignored that some studies have even reported better oncological results in patients operated by laparoscopic approach (15,26,27,31).

One of the key points related to those differences in morbidity and mortality that had been demonstrated by Fretland et al (32) in the context of a substudy within the OsloCoMet study (16), which shows that LLR of CRLMs reduced the inflammatory response compared with open resection. Our study shows similar results and although statistical significance is lost after PSM, there are obvious differences in both survival curves. In this context, a possible explanation for the possible better oncological results of LLR could be a reduced inflammatory response (32), lower morbidity and better early functional recovery compared to the OLR; allowing a shorter interval to postoperative chemotherapy as it is reported in a recent study from Tohme et al (33).

While that fact that this study is based only in a single centre could be considered a limitation, this characteristic also provides advantages such as a high degree of standardization of diagnostics, patient selection, surgical technique and postoperative care, all based in a high-volume hepatobiliary centre with extensive open and laparoscopic experience. Additionally, it must be borne in mind that study sample size decreased after PSM, which could have affected the accuracy of overall and survival-estimated data. Another limitation is that this study is not an RCT. However, use of a well-designed PSM analysis allows critical consideration of this available data, bearing in mind the caveat of possible confounding factors potentially affecting results.

5. Conclusions

LLR is a beneficial alternative to OLR in selected patients with CRLM, providing favourable short-term outcomes such as reduced blood loss, shorter length of ITU and hospital stay. LLR does not compromise oncological outcomes including surgical margin, overall-survival and disease-free survival. Our results support that LLR should be preferred for patients presenting with resectable CRLM.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2021;71(3):209–49. DOI: 10.3322/caac.21660
2. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006; 93: 465-474. DOI: 10.1002/bjs.5278
3. Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235: 759–66. DOI: 10.1097/00000658-200206000-00002.
4. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. Arch Surg. 2004;139: 1168–72. DOI: 10.1001/archsurg.139.11.1168.
5. Cummings LC, Payes JD, Cooper GS. Survival after hepatic resection in metastatic colorectal cancer: a population-based study. Cancer 2007;109:718–26. DOI: 10.1002/cncr.22448.
6. Reich, H.; McGlynn, F.; DeCaprio, J.; Budin, R. Laparoscopic excision of benign liver lesions. Obstet. Gynecol. 1991, 78 Pt 2, 956–958. PMID: 1833688
7. Katkhouda, N.; Fabiani, P.; Benizri, E.; Mouiel, J. Laser resection of a liver hydatid cyst under videolaparoscopy. Br. J. Surg. 1992, 79, 560–561. DOI: 10.1002/bjs.1800790628
8. Koffron, A., Geller, D., Gamblin, T. C. & Abecassis, M. Laparoscopic liver surgery: Shifting the management of liver tumors. Hepatology. 44, 1694–1700, DOI:10.1002/hep.21485 (2006).
9. Jackson NR, Hauch A, Hu T, Buell JF, Slakey DP, Kandil E. The safety and efficacy of approaches to liver resection: a meta-analysis. JSLS 2015; 19: e2014·00186. DOI: 10.4293/JSLS.2014.00186
10. Schiffman SC, Kim KH, Tsung A, Marsh JW, Geller DA. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. Surgery 2015; 157: 211–222. DOI: 10.1016/j.surg.2014.08.036
11. Koffron AJ, AuffenbergG,Kung R,Abecassis M. Evaluation of 300 minimally invasive liver resections at a single institution: less is more. Ann Surg. 2007;246:385–92. DOI: 10.1097/SLA.0b013e318146996c
12. Simillis C, Constantinides VA, Tekkis PP, Darzi A, Lovegrove R, Jiao L, et al. Laparoscopic versus open hepatic resections for benign and malignant neoplasm meta-analysis. Surgery. 2007;141:203–11. DOI: 10.1016/j.surg.2006.06.035
13. Nguyen KT, Marsh JW, Tsung A, Steel JJ, Gamblin TC, Geller DA. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. Arch Surg. 2011;146:348–56. DOI: 10.1001/archsurg.2010.248
14. Rao A, Rao G, Ahmed I. Laparoscopic or open liver resection? Let systematic review decide it. Am J Surg. 2012;204:222–31. DOI: 10.1016/j.amjsurg.2011.08.013
15. Castaing D, Vibert E, Ricca L, Azoulay D, Adam R, Gayet B. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. Ann Surg 2009; 250: 849–855. DOI: 10.1097/SLA.0b013e3181bcaf63
16. Fretland, A.A.; Dagenborg, V.J.; Bjornelv, G.M.W.; Kazaryan, A.M.; Kristiansen, R.; Fagerland, M.W.; Hausken, J.; Tonnessen, T.I.; Abildgaard, A.; Barkhatov, L.; et al. Laparoscopic versus open resection for colorectal liver metastases: The OSLO-COMET randomized controlled trial. Ann. Surg. 2018; 267; 199–207. DOI: 10.1097/SLA.0000000000002353
17. Austin, P.C. An introduction to propensity score methods for reducing the e
ects of confounding in observational studies. Multivar. Behav. Res. 2011; 46; 399–424. DOI: 10.1080/00273171.2011.568786
18. Adamina, M.; Guller, U.; Weber, W.P.; Oertli, D. Propensity scores and the surgeon. Br. J. Surg. 2006; 93; 389–394. DOI: 10.1002/bjs.5265
19. Tzanis D, Shivathirthan N, Laurent A, Abu Hilal M, Soubrane O, Kazaryan AM, et al. European experience of laparoscopic major hepatectomy. J Hepatobiliary Pancreat Sci 2013;20:120-124. DOI: 10.1007/s00534-012-0554-2
20. Ciria R, Cherqui D, Geller DA, et al. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. Ann Surg. 2016;263:761-77. [PMID: 26700223] DOI: 10.1097/SLA.0000000000001413
21. Cipriani F, Rawashdeh M, Stanton L, et al. Propensity score–based analysis of outcomes of laparoscopic versus open liver resection for colorectal metastases. Br J Surg. 2016;103(11): 1504-1512. DOI: 10.1002/bjs.10211
22. Montalti R, Berardi G, Laurent S, Sebastiani F, Ferdinande L, Libbrecht LJ et al. Laparoscopic liver resection compared to open approach in patients with colorectal liver metastases improves further resectability: oncological outcomes of a case–control matched-pairs analysis. Eur J Surg Oncol 2014; 40: 536–544. DOI: 10.1016/j.ejso.2014.01.005

23. Untereiner X, Cagniet A, Memeo R, Tzedakis S, Piardi T, Severac F, et al. Laparoscopic hepatectomy versus open hepatectomy for colorectal cancer liver metastases: comparative study with propensity score matching. Hepatobiliary Surg Nutr [Internet]. 2016;5(4):290–9. DOI: 10.21037/hbsn.2015.12.06
24. Ratti F, Fiorentini G, Cipriani F, Catena M, Paganelli M, Aldrighetti L. Laparoscopic vs open surgery for colorectal liver metastases. JAMA Surg [Internet]. 2018;153(11):1028–35. DOI: 10.1001/jamasurg.2018.2107
25. Beppu T, Wakabayashi G, Hasegawa K, Gotohda N, Mizuguchi T, Takahashi Y, et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for colorectal liver metastases with propensity score matching: a multi-institutional Japanese study. J Hepatobiliary Pancreat Sci [Internet]. 2015;22(10):711–20. DOI: 10.1002/jhbp.261.
26. Kazaryan AM, Marangos IP, Røsok BI, Rosseland AR, Villanger O, Fosse E et al. Laparoscopic resection of colorectal liver metastases: surgical and long-term oncologic outcome. Ann Surg 2010; 252: 1005–1012. DOI: 10.4251/wjgo.v13.i7.732
27. Zhang X-L, Liu R-F, Zhang D, Zhang Y-S, Wang T. Laparoscopic versus open liver resection for colorectal liver metastases: A systematic review and meta-analysis of studies with propensity score-based analysis. Int J Surg [Internet]. 2017;44:191–203. DOI:
28. Robles-Campos R, Lopez-Lopez V, Brusadin R, Lopez-Conesa A, Gil-Vazquez PJ, Navarro-Barrios Á, et al. Open versus minimally invasive liver surgery for colorectal liver metastases (LapOpHuva): a prospective randomized controlled trial. Surg Endosc [Internet]. 2019;33(12):3926–36. DOI: 10.1007/s00464-019-06679-0
29. Wong-Lun-Hing EM, van Dam RM, van Breukelen GJP, Tanis PJ, Ratti F, van Hillegersberg R, et al. Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study). Br J Surg [Internet]. 2017;104(5):525–35. DOI: 10.1002/bjs.10438
30. Berardi G, Van Cleven S, Fretland ÅA, et al. Evolution of laparoscopic liver surgery from innovation to implementation to mastery: perioperative and oncologic outcomes of 2,238 patients from 4 European specialized centers. *J Am Coll Surg*. 2017;225(5):639-649. DOI: 10.1016/j.jamcollsurg.2017.08.006
31. Parks KR, Kuo YH, Davis JM, O' Brien B, Hagopian EJ. Laparoscopic versus open liver resection: a meta-analysis of long-term outcome. HPB (Oxford). 2014;16:109–18. DOI: 10.14701/ahbps.2021.25.1.1
32. Fretland AA, Sokolov A, Postriganova N, Kazaryan AM, Pischke SE, Nilsson PH, et al. Inflammatory response after laparoscopic versus open resection of colorectal liver metastases: Data from the Oslo-CoMet trial. Medicine (Baltimore) [Internet]. 2015;94(42):e1786. DOI: 10.1097/MD.0000000000001786
33. Tohme S, Goswami J, Han K, et al. Minimally invasive resection of colorectal cancer liver metastases leads to an earlier initiation of chemotherapy compared to open surgery. J Gastrointest Surg. 2015;19(12):2199-2206. DOI:10 .1007/s11605-015-2962-5