Long-term survival in laparoscopic vs open resection for colorectal liver metastases: inverse probability of treatment weighting using propensity scores

Joel W. Lewin1, Nicholas A. O’Rourke1,2, Adrian K.H. Chiow1, Richard Bryant1,3, Ian Martin2, Leslie K. Nathanson2,3 & David J. Cavallucci1,2

1Hepato-Pancreato-Biliary Surgery, Royal Brisbane & Women’s Hospital, 2General Surgery, The Wesley Hospital, and 3General Surgery, Holy Spirit Northside Hospital, Australia

Abstract

Background: This study compares long-term outcomes between intention-to-treat laparoscopic and open approaches to colorectal liver metastases (CLM), using inverse probability of treatment weighting (IPTW) based on propensity scores to control for selection bias.

Method: Patients undergoing liver resection for CLM by 5 surgeons at 3 institutions from 2000 to early 2014 were analysed. IPTW based on propensity scores were generated and used to assess the marginal treatment effect of the laparoscopic approach via a weighted Cox proportional hazards model.

Results: A total of 298 operations were performed in 256 patients. 7 patients with planned two-stage resections were excluded leaving 284 operations in 249 patients for analysis. After IPTW, the population was well balanced. With a median follow up of 36 months, 5-year overall survival (OS) and recurrence-free survival (RFS) for the cohort were 59% and 38%. 146 laparoscopic procedures were performed in 140 patients, with weighted 5-year OS and RFS of 54% and 36% respectively. In the open group, 138 procedures were performed in 122 patients, with a weighted 5-year OS and RFS of 63% and 38% respectively. There was no significant difference between the two groups in terms of OS or RFS.

Conclusion: In the Brisbane experience, after accounting for bias in treatment assignment, long term survival after LLR for CLM is equivalent to outcomes in open surgery.

Received 12 August 2015; accepted 21 August 2015

Correspondence

Joel W. Lewin, Royal Brisbane Hospital, Butterfield Street, Herston, QLD, 4006, Australia. E-mail: joel.lewin@uqconnect.edu.au

Introduction

The liver is the most common non-nodal site affected by colorectal cancer metastases, with approximately 60% of all patients having developed liver metastases by 5 years following diagnosis. The role of hepatectomy for colorectal liver metastases (CLM) is well established, with open resection series reporting 5-year overall survival (OS) between 37 and 45%.

The application of laparoscopy to liver resection for malignancy remains somewhat controversial in the absence of randomised controlled trials to confirm oncologic equivalence to the open approach. With increasing experience and wider application of laparoscopic liver resection (LLR), much enthusiasm has been directed towards its use in CLM. Since the initial reports of LLR in the early nineties, there has been a steady increase in its use for both benign and malignant conditions. A recent study on the international experience with laparoscopic liver resection at 11 experienced centers reported 5388 LLRs and 1184 major LLRs, over half of which were for malignancy.

The short term benefits of a laparoscopic approach to liver resection compared to open are well described, including reduced postoperative pain and analgesia requirement, smaller incisions, less wound complications, reduced hospital length of stay (LOS) and even reduced overall cost. There is, however, a relative paucity of quality studies comparing survival and long-term outcomes for open versus laparoscopic resection of CLM.
Our unit began LLR for CLM in 1999, with the first laparoscopic right hepatectomy performed in 2000. A randomised controlled trial (RCT) comparing laparoscopic to open hepatectomy for malignancy remains difficult to achieve, therefore this study attempts to maximise the utility of collected observational data by using statistical tools that enable balance across treatment and control groups.

Propensity score-based analyses have grown in popularity in recent years, in large part due to the promise of reducing confounding inherent in observational cohort studies. Inverse probability of treatment weighting (IPTW) using the propensity score has a number of potential advantages over more common matching techniques. Evaluating data using these models adds some statistical complexity, however if well specified, can allow estimation of causal effects from observational data.

Method

Patient selection

Ethics approval was obtained for a retrospective review of prospectively collected data, involving patients undergoing liver resection for CLM from 2000 to 2014. Five surgeons (NO’R, LN, IM, RB, DC) at three Brisbane institutions (RBWH, TWH, HSNH) during that period performed all operations. Patient demographics, operative details and data on both intraoperative and postoperative adverse events were recorded prospectively from 2004 in a secure hepatic surgery database. Data from before this period was obtained retrospectively. Details of the colorectal primary (size, location, lymph node status, differentiation and operative details), burden of liver disease (tumour number, location, diameter, total tumour volume) and CEA were collected. Clinical Risk Scores and pre- and postoperative Basingstoke Predictive Index (BPI) scores were determined from their component factors at the time of data analysis.

Preoperative patient management

Diagnosis of liver metastases was made with either high definition, multiphase, computed tomography (CT) or more recently, magnetic resonance imaging (MRI) with liver specific contrast (Gd-EOB-DTPA, Primovist™ or Eovist™). Positron emission tomography (PET) imaging was used routinely since becoming available in 2004, to exclude extrahepatic disease.

Patients were discussed at a multidisciplinary team meeting (MDT). Pseudo-neoadjuvant and/or adjuvant chemotherapy was used as per consensus after discussion at MDT. Whether a patient was to receive open or laparoscopic resection had no influence on the overall chemotherapy approach determined at MDT. All surgeons had experience in, and offered both laparoscopic and open surgery. If the projected remnant liver was less than 30% of total liver volume, if the risk of postoperative liver insufficiency was high, or if patients had resectable bilobar disease, portal vein embolisation or ligation, and/or 2-step staged hepatectomy was used.

Operative techniques

Over the study period, techniques of both laparoscopic and open liver surgery have evolved. Open liver resection was performed using standard techniques. For major hepatectomy, extrahepatic division of the portal vein, hepatic artery and hepatic veins with parenchymal transection using CUSA™ (Cavitron Ultrasonic Surgical Aspirator, Tyco Healthcare, Mansfield, MA, USA) was most commonly used.

Most laparoscopic resections were performed in a “pure” fashion, with specimen extraction following the end of the heptectomy via a Pfannenstiel incision or extension of the umbilical port site. Occasionally, “hybrid” and “hand-assisted” techniques were performed. Laparoscopic ultrasound was performed to confirm the number and location of lesions. Parenchymal division has evolved from the use of stapling devices and Harmonic Shears® (Ethicon Endo-Surgery, Cincinnati, OH, USA) to “hot” Kelly-clysis using a laparoscopic dolphin tip Ligasure™ (Covidien, Mansfield, MA) with copious irrigation. Hem-o-lok® clips (Weck Surgical Instruments, Teleflex Medical, Durham, NC) were used for vascular control with occasional stapler use for larger vessels.

The Brisbane terminology was used for classifying all liver resections. Intraoperative complications were classified as grade I, II or III, based on the Satava classification of intraoperative incidents adapted for LLR.

Postoperative management

Patients were occasionally admitted to ICU postoperatively, based on the presence of significant preoperative comorbidities or intraoperative surgical or anaesthetic complications. Standard postoperative cares included chemical and mechanical DVT prophylaxis, postoperative analgesia, monitoring of liver function and early mobilisation. Postoperative analgesia was most often intravenous patient-controlled analgesia and non-steroidal anti-inflammatories. Epidural and single-shot intrathecal analgesia were used occasionally.

Postoperative complications were graded and recorded using the Dindo-Clavien classification. Routine postoperative follow-up consisted of clinical assessment and CEA levels at 3, 6, 12, 18 and 24 months, then annually, with imaging performed at 6 monthly intervals or sooner, if indicated. Recurrent disease was diagnosed on imaging and included disease at extrahepatic sites. RFS was defined as time from resection until the development of a recurrence, either hepatic or extrahepatic, or death. OS was measured from study entry until death (any cause).

Statistics and survival analysis

Data was considered on an intention-to-treat (ITT) basis, such that patients who required conversion to hand assist, hybrid or open approach, were included in the laparoscopic group. Propensity scores were generated using generalised boosted modelling (GBM) logistic regression modelling. Based on available evidence, preoperative baseline covariates were selected to
calculate propensity scores. Age, sex, planned major resection status, maximum lesion diameter, number of lesions, bilateral lesions, primary T stage, primary N stage, primary tumour grade, previous chemotherapy, time since primary resection and difficult tumour location (segments 1, 4a, 7, 8) were determined as the important measurable variables affecting treatment selection. Note that only covariates available prior to surgery are used to calculate the propensity score, as the aim is to create a balanced population for treatment selection, not for outcome assessment. To minimise the impact of missing data, multiple imputation using chained equations (MICE) (using classification and regression trees to generate five complete data sets) was performed. After Hill,24 statistics were generated as pooled estimates across the imputed data sets using Rubin’s rules.25

GBM

GBM-based logistic regression is a non-parametric method that algorithmically calculates an optimal model of treatment assignment based on the selected covariates and their interactions (two-way in this case). It is a widely used machine learning technique throughout the social sciences and industry. It was chosen over simple logistic regression as recent studies of PS estimation have shown superior performance in terms of bias reduction and mean-squared error26 with machine learning techniques. Additional advantages include the ability to handle highly correlated variables and eliminating the need for scaling and normalisation. It allows modelling of complex, non-linear relationships between treatment assignment and important covariates.

GBM models require some tuning to achieve balance. Model optimisation was achieved by minimising the largest Kolmogorov–Smirnov (KS) statistic of the covariates. The average treatment effect (ATE) was used to generate a balanced population. This provides the best possible comparator to a randomised control trial where we wish to estimate the average effect of moving the entire population from untreated (open) to treated (laparoscopic). It differs from matching on the PS, which provides an estimate of the average effect of the treatment (ITT) on the population that ultimately received the treatment. Balance was analysed by assessing the average standardised absolute mean difference (ASAM) defined as the treatment group mean minus the control group mean divided by the pooled sample standard deviation. Values less than 0.2 represent small differences between groups, 0.2–0.4 moderate, and >0.6 large.27

IPTW with the propensity score

The propensity score (PS) is defined as the probability that a patient would be assigned to a particular treatment conditional on the observed baseline covariates. This probability is known by design in RCTs, but in the observational setting it must be estimated. There are a number of propensity score estimation methods available and different ways of applying the score once calculated: stratification, matching, weighting and covariate adjustment.28 Matching and weighting are the most common as both have been shown to have superior performance to the other methods for most common situations. An important aspect is specification of the target “estimand”. Pair matching methods will, by definition, estimate the average effect of treatment on those who ultimately received the treatment (so called “ATT”). The ATT-based PS looks at the effect of the treatment only as it applies to those who actually received it – i.e. what was the effect of laparoscopy compared with open for patients similar to those who had a laparoscopic procedure? This occurs because we start with a group of treated patients and match controls that have similar baseline covariates (and hence a similar PS). This differs from a RCT, which estimates the average effect of moving an entire group from untreated to treated (so called “ATE”). The ATE looks at the effect of laparoscopy if it could be applied to all patients in the sample, and can be estimated with techniques such as IPTW using PS. IPTW generates a single pseudo-population in which the balance of pre-treatment covariates is similar (as in a RCT) and therefore allows a stronger statement of causation to be made.

Following propensity score generation, stabilised inverse probability of treatment weights (IPTW) were calculated. For pre-treatment covariates where the balance estimates remained of concern (ASAM >0.2), double-robust (DR) Cox proportional hazards regression was performed. DR Cox combines regression and PS weights such that any bias due to small imbalances that persist after weighting can be accounted for via subsequent regression.29–31

All statistical analyses were performed with R v3.1.031 using the survival,32 twang,33 survey34 and mice35 packages. Overall survival (OS) was defined as time to death by any cause, and recurrence free survival (RFS) as time to recurrence (any location) or death by any cause.

Further details of the modelling and propensity scores, including R code for the performed analyses, can be found in the statistical supplement or linked at https://dcava.github.io/wpp.

Results

Perioperative outcomes

After excluding seven patients with planned two-stage hepatectomy, a total of 146 LLRs and 138 open resections were carried out in 262 patients. 222 patients had a single operation and 27 had two or more liver resections. 13 (8.9%) laparoscopic resections were converted to an open procedure due to adhesions (n = 3), haemorrhage (n = 6) and failure to progress (n = 4). 1 patient (0.7%) was converted to a hybrid procedure due to equipment failure and another converted to hand assist (0.7%) due to failure to progress. To maintain a conservative estimate of treatment effect, 10 patients (6.8%) who had hybrid operations and 2 (1.4%) with hand assisted procedures were included as laparoscopic procedures. The types of resections performed are summarised in Table 1.
In the laparoscopic group, all intraoperative adverse events were due to grade I haemorrhage (n = 7), with no grade II or III events. In the open group, grade I (n = 5) and grade II (n = 1) adverse events were all bleeding related. One patient had a grade III event due to complete common bile duct transection, requiring return to theatre for hepaticojejunostomy. Postoperative complications are detailed in Table 3. There was no mortality (30-day or in-hospital) after laparoscopic resection. Two postoperative deaths occurred after open resection (1.4%); one patient from an aspiration pneumonia and one due to postoperative hepatic failure.

A comparison of weighted and unweighted postoperative outcomes are shown in Table 4. Median operation time (p < 0.0001), HLOS (p < 0.0006), blood loss (p < 0.0001) and positive margin frequency (p = 0.03) were significantly reduced following laparoscopic surgery compared to open.

Due to the small number of patients having more than two resections (n = 6), estimates for these resections were unstable and therefore subsequent resections (greater than two) are considered the same as a second resection – the data is still included in OS and RFS calculation, however it is not possible to separate the effect of having two resections from having three or four. Similarly, the small number of primary T1 tumours necessitated their incorporation into the same group as T2 tumours, forming a combined T1/T2 group.

**Balance diagnostics**
Significant differences exist between the laparoscopic and open groups at baseline (Table 2). The proportion of patients planned for major resection, with tumours in difficult locations or with multiple lesions was significantly greater in the open resection group. Following IPTW, there was good balance across all covariates, with no statistically significant differences remaining.

The impressive change following weighting can be seen in Supplement Fig. 1. The Quantile–Quantile plot (Supplement Fig. 2) provides another visual assessment of balance. The diagonal line represents the expected distribution of p-values from independent tests. Significant deviation of values below diagonal suggests lack of balance whilst p-values on or above suggests balance might have been achieved.

**Table 1** Type of Liver Resections (based on main resection per procedure)

<table>
<thead>
<tr>
<th>Type of resection</th>
<th>Laparoscopic</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical</td>
<td>46</td>
<td>12</td>
</tr>
<tr>
<td>Hemihepatectomy</td>
<td>39</td>
<td>95</td>
</tr>
<tr>
<td>Segmentectomy/bisectionectomy</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Non-anatomic</td>
<td>26</td>
<td>8</td>
</tr>
</tbody>
</table>

a Can include additional segmentectomy/bisectionectomy or tumorectomy.
b Procedures involving non-anatomic resection only.

Whilst not “statistically” significant, the indicators of major resection, bilaterality, lesion count and primary N-stage remain imperfectly balanced with ASAM >0.2 (Table 2). These covariates were included in a double-robust Cox regression model to ensure that any residual bias did not impact the estimate for treatment effect. The hazard ratios for the laparoscopic approach with double-robust correction (HR 0.98 95% CI 0.53–1.81) and treatment only models (HR 0.96, 95% CI 0.53–1.68) for overall survival did not differ and none of the included covariates had coefficients with significant effect, suggesting that the propensity score model was well specified, with minimal residual bias despite persistent small imbalances.

**Oncological & survival outcomes**
Median follow-up was 36 months. Weighted Kaplan–Meier survival analysis showed no difference in 5 year OS (54% vs 63%, generalised Wilcoxon test p = 0.66) or median OS (118 vs 101 months) between the laparoscopic and open groups respectively (Fig. 1a). 5 year RFS (36% vs 38%, generalised Wilcoxon test p = 0.5) did not differ between the laparoscopic and open groups (Fig. 1b). Stratified by procedure number, the median survival after the first liver resection was 33 months (95% CI 25–61) and after subsequent resections was 24 months (95% CI 14–∞) for the whole cohort. There was no significant difference between the laparoscopic or open groups. The double-robust Cox proportional hazard ratios for OS and RFS for the laparoscopic approach were HR 0.98 (95% CI 0.53–1.81) and 1.04 (95% CI 0.69–1.59).

Whilst the major purpose of this study was to analyse outcomes based on treatment assignment alone (after generating a balanced sample), multivariate IPTW Cox proportional hazards models were generated for both OS and RFS based on covariates that were important on univariate analysis, including primary T and N stage, bilaterality, lesion count, major procedure, blood loss, margin status, length of hospital stay and operative time (Table 2). The hazard ratio for surgical approach was unaffected by multivariate adjustment. A primary T4 lesion was a strong predictor of both poor OS (HR 6.97, 95% CI 1.79–27.22) and RFS (HR 2.67, 95% CI 1.09–6.51). The effect of hospital length of stay was small but significant, with an increased risk of death or recurrence of approximately 5% for each additional day in hospital over the mean LOS (approximately 8 days). This likely represents a proxy marker for the occurrence of postoperative complications. The presence of bilateral lesions had an impact on RFS (HR 1.72, 95% CI 1.05–2.83) but not OS, leading to an increase in the rate of recurrence of over 70% compared with those without bilateral lesions.

**Discussion**
Liver resection, along with systemic chemotherapy, offers long-term survival in patients with CLM. In considering a minimally invasive approach to surgery for any cancer, surgical and oncological safety remain the guiding principles. Laparoscopic...
surgery offers obvious benefits in short term outcomes, but it is important to demonstrate that long term cancer outcomes are at least equivalent to those achieved with open surgery. In the absence of prospective RCTs, clinicians must rely on comparative studies; however there will always be bias in such studies. In particular, there may be significant bias in treatment assignment – the very effect we are trying to measure. This is particularly the case in LLR, where most surgeons begin their experience with simple cases and generally follow international consensus guidelines for patient selection. In this report of our experience with laparoscopic and open resection of CLM over the last 14 years, we have attempted to maximise the utility of our observational data using IPTW to account for such bias.

With good balance after weighting, 5-year OS and RFS were comparable between laparoscopic and open groups. These results are consistent with previous smaller, case-controlled, comparative studies36–40 (Supplement Table 1) and a recent meta-analysis,41 confirming that a laparoscopic approach to hepectectomy is oncologically equivalent to open. Following weighted, multivariate adjustment, the T-stage of the primary (in particular T4) was a consistent predictor of increased risk of death and early recurrence in our population, as were bilateral lesions. Both of these factors have been linked to poor outcomes in past analyses.

Despite the growing application of laparoscopy to liver resection for malignancy, no RCT has been published to confirm comparable oncological outcomes between laparoscopic and open approaches. Oft-quoted technical concerns regarding the laparoscopic approach include the loss of tactile inspection of the liver and peritoneal cavity,42 risk of gas embolism and difficulty in controlling catastrophic bleeding.43 No grade III intra-operative haemorrhage or complications from gas embolism

| Table 2 Balance of preoperative covariates for unweighted and weighted data (mean values) |
|------------------------------------------|----------|----------------|------|----------------|----------|----------------|------|----------------|----------|
| Unweighted | Weighted |
| Laparoscopic | Open | ASAM p | Laparoscopic | Open | ASAM p |
| Age | 63.36 | 60.49 | 0.25 | 0.04 | 63.05 | 61.35 | 0.15 | 0.25 |
| Sex(female) | 0.40 | 0.33 | 0.16 | 0.17 | 0.38 | 0.34 | 0.08 | 0.55 |
| CEA | 35.24 | 51.74 | −0.11 | 0.37 | 35.96 | 54.92 | −0.13 | 0.31 |
| Major resection | 0.27 | 0.69 | −0.84 | 0.00 | 0.42 | 0.54 | −0.23 | 0.10 |
| Difficult location | 0.34 | 0.56 | −0.43 | 0.00 | 0.42 | 0.46 | −0.09 | 0.52 |
| Bilateral | 0.11 | 0.27 | −0.41 | 0.00 | 0.14 | 0.22 | −0.21 | 0.13 |
| Maximum diameter | 32.29 | 41.85 | −0.34 | 0.00 | 34.13 | 38.32 | −0.16 | 0.23 |
| Number of lesions | 1.47 | 2.13 | −0.48 | 0.00 | 1.60 | 1.88 | −0.22 | 0.10 |
| Primary lesion: | | | | | | | | |
| Mod differentiated | 0.77 | 0.64 | 0.31 | 0.04 | 0.75 | 0.66 | 0.20 | 0.39 |
| Poorly differentiated | 0.19 | 0.27 | −0.19 | 0.20 | 0.27 | −0.16 |
| Well differentiated | 0.03 | 0.09 | −0.29 | 0.04 | 0.07 | −0.10 |
| T1/T2 | 0.27 | 0.23 | 0.09 | 0.72 | 0.26 | 0.23 | 0.07 | 0.74 |
| T3 | 0.53 | 0.56 | −0.06 | 0.55 | 0.54 | 0.01 |
| T4 | 0.20 | 0.21 | −0.03 | 0.19 | 0.23 | −0.10 |
| N0 | 0.42 | 0.35 | 0.16 | 0.00 | 0.38 | 0.36 | 0.05 | 0.40 |
| N1 | 0.30 | 0.49 | −0.44 | 0.34 | 0.46 | −0.24 |
| N2 | 0.19 | 0.14 | 0.12 | 0.20 | 0.14 | 0.14 |
| N3 | 0.09 | 0.01 | 0.26 | 0.08 | 0.04 | 0.14 |
| Years from primary | | | | | | | | |
| 0 | 0.03 | 0.02 | 0.07 | 0.39 | 0.03 | 0.02 | 0.08 | 0.60 |
| 1 | 0.47 | 0.36 | 0.22 | 0.47 | 0.40 | 0.14 |
| 2 | 0.27 | 0.34 | −0.17 | 0.26 | 0.33 | −0.16 |
| 3 | 0.09 | 0.09 | 0.01 | 0.09 | 0.08 | 0.04 |
| 4 | 0.04 | 0.07 | −0.16 | 0.04 | 0.07 | −0.18 |
| 5 | 0.10 | 0.12 | −0.07 | 0.11 | 0.11 | 0.02 |
| Previous chemotherapy | 0.28 | 0.34 | −0.13 | 0.28 | 0.27 | 0.36 | −0.19 | 0.18 |

ASAM, average standardised absolute mean difference.
occurred in the laparoscopic group, suggesting initial concerns regarding the effects of pneumoperitoneum and the safety of applying laparoscopy to liver resection have not been realised in this cohort. Similarly, there were no port site metastases and perioperative complications were comparable between groups.

The requirement of tactile palpation of the liver has, in our experience, been obviated by the routine use of high quality preoperative MRI and intraoperative ultrasound. Although there were no deaths as a consequence of catastrophic haemorrhage in the laparoscopic group, it should be stressed that these results are the product of extensive experience with laparoscopic liver surgery, evolved over nearly two decades. Without adequate training, experience and operative care during minimally invasive liver surgery, disasters can occur.

Studies are increasingly emerging that demonstrate acceptable long term survival following LLR for CLM. The generalisability of cohort comparison studies is limited by the bias due to inherent differences between the non-randomised treated and untreated subjects. The use of propensity scores has increased in the scientific literature in recent years since the method was first published by Rosenbaum and Rubin as a way of accounting for these differences in treatment assignment.

PS based techniques have much to offer, but come with their own assumptions and limitations. Model specification, estimand selection, balance diagnostics and matching technique all influence the final interpretation of the model. Specifying all potentially important baseline covariates, while ensuring that only preoperative variables are included, is a necessity, but to an extent must rely on current evidence and expert opinion for definition. Estimand selection (ATT or ATE) is important as it defines the study question and the generalisability of the results.

Commonly, the PS is estimated using multivariate logistic regression and subsequently used to create matched cohorts. Recent studies have shown that machine learning techniques such as the GBM used here, have superior performance to logistic regression for generation of the PS. Matching often comes at the cost of reduced sample size, which is particularly important in survival analysis where small samples with low event rates may lead to biased estimates.

By contrast, IPTW keeps information from most, if not all patients, by exaggerating the importance of patients where, for example, their baseline covariates would suggest they are likely to receive the control but they in fact receive the treatment. This creates a “pseudo” sample “in which the distribution of measured baseline covariates is independent of treatment assignment.”

One covariate not captured completely in our model is “technical difficulty”. Whilst proxies such as tumour location and size can be used, these markers may not fully capture complexities such as proximity to inflow or outflow structures. The fact that the laparoscopic group had approximately half the positive

Table 4 Unweighted and weighted univariate postoperative outcomes

<table>
<thead>
<tr>
<th>Postoperative variable</th>
<th>Unweighted</th>
<th>Weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated blood loss (mL)</td>
<td>Laparoscopic</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Open</td>
<td>600</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Operation time (mins)</td>
<td>120</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive margin frequency</td>
<td>12 (8%)</td>
<td>25 (18%)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.031</td>
</tr>
<tr>
<td>Margin distance (mm)</td>
<td>5</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>0.178</td>
</tr>
</tbody>
</table>

*Median; *Chi square test of proportions.
margin rate (8% vs 18%) does raise the spectre of unexplained complexity reserved for the open group. The major limitation however, is that a non-randomised study cannot fully account for unobserved differences between groups, and this remains the most significant limitation of this analysis.

Patients who had unresectable hepatic or extrahepatic disease at initial presentation were not captured by this analysis, as the primary goal of the study was to compare survival in resectable disease. An area often posed as a limitation to studies such as this, is failing to factor in the effect of changing and improving neoadjuvant and adjuvant chemotherapy regimes in the survival analysis. The case mix in this study of laparoscopic and open resections on a per-year basis were evenly matched, so both groups of patients received the most effective chemotherapy regimens available at the time of their disease. The surgical approach did not influence the selection of neoadjuvant or adjuvant treatments applied. Laparoscopic liver surgery for malignancy is here to stay. This study has shown, after accounting for the various types of bias associated with observational studies, that LLR for CLM is at least oncologically equivalent to open resection, with comparable long term survival.

Figure 1 (a) Weighted overall mortality and (b) recurrence or death for laparoscopic vs open resections

Sources of funding
Nil to declare.

Conflicts of interest
None declared.

References


**Appendix A. Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2015.08.001.