Management of Colorectal cancer with Synchronous liver Metastases: An Inception Cohort Study (CoSMIC).

Anthony KC Chan PhD[1], James M Mason DPhil[2], Minas Baltatzis PhD[1] & Ajith K Siriwardena MD[1,3] on behalf of the CoSMIC collaborators.

[1]Regional Hepato-Pancreato-Biliary Unit, Manchester Royal Infirmary, Manchester UK.

[2]Warwick Medical School, The University of Warwick, Coventry, UK

[3]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK.

Corresponding Author:

Professor Ajith K Siriwardena MD FRCS,

Regional Hepato-Pancreato-Biliary Unit,

Manchester Royal Infirmary, Manchester M13 9WL, United Kingdom.

Tel: +44 161 276 8766

Fax: +44 161 276 4530

Email: ajith.siriwardena@mft.nhs.uk

Funding support: AKCC was supported by a grant from the Dickinson Trust.

Running head: Colorectal cancer with liver metastases

Mini-abstract

CoSMIC is a prospective cohort study evaluating pathway-specific outcomes in patients with colorectal cancer and synchronous liver metastases treated by surgery and systemic chemotherapy with all three modern surgical pathways utilised. There was no difference in critical care or in-patient stay between pathways. Failure to complete pathway was seen most frequently in the liver-first group.

[word count 55].

Structured abstract

Objective

CoSMIC is the first prospective study evaluating pathway-specific outcomes in patients with colorectal cancer and synchronous liver metastases treated by surgery and contemporary systemic chemotherapy with all three modern surgical pathways being utilised.

Summary background data

Approximately one fifth of patients with colorectal cancer present with hepatic metastases. There are limited prospective data on outcomes of surgery by synchronous, liver-first or bowel-first routes where chemo(radio)therapy is integrated into management.

Methods

Between 1st April 2014 and 31st March 2017, 238 patients with colorectal cancer and synchronous liver metastases were assessed. After exclusions, 125 patients constitute the study population. Data are reported on pathway-specific outcomes including complications, treatment completion, overall and disease-free survival. The study was registered with clinical trials.gov (NCT 02456285).

Results

There was no difference in age, body mass index, or Charlson score between surgical groups. Neoadjuvant chemotherapy was used in 50 (40%) patients for a mean duration of 4.6 months (standard deviation [SD] 5.4), and mean time from completion of chemotherapy to surgery was 2.6 months (SD 1.9). Complications were similar between patients completing the synchronous and staged pathways (p = 0.66). Mean total inpatient stay was 16.5 days (SD 8.1) for staged surgery compared with 16.8 days (SD 10.3) for the synchronous group (t-test; p = 0.91). There was no difference in time to treatment completion between pathways. Thirty six (35%) patients were disease-free at 12 months, with no significant difference between groups (Chi-square, p = 0.448). Quality of life was similar in all surgical groups.

Conclusion

Perioperative complications and oncological and healthcare occupancy outcomes are equivalent between patients completing staged and synchronous pathways for the management of patients with colorectal cancer and synchronous liver metastases. Future studies should focus on optimizing the criteria for pathway selection, incorporation of cancer genomics data, and patient (user) preferences.

Introduction

Approximately one fifth of patients with colorectal cancer will present with metastases either predominantly or exclusively in the liver.[1,2,3] Treatment typically comprises a combination of systemic chemotherapy and surgery directed at removal of disease at both the primary and metastatic sites.[4,5] For those presenting with resectable disease either confined to the liver or predominantly hepatic metastases there are three surgical treatment pathways.[1,4] These are synchronous liver and bowel cancer resection during a single operative procedure or a staged approach either as bowel-first surgery followed by liver resection or as a liver-first procedure followed by bowel cancer resection.[6-8] Systemic chemotherapy is integrated with surgery with both the National Comprehensive Cancer Network (NCCN) guidance and the European Society of Medical Oncology (ESMO) placing chemotherapy as a proximal pathway treatment in patients with extensive or surgically "unfavourable" disease and surgery being placed earlier in patients with resectable disease.[9,10] Treatment has to balance patient-level factors (co-morbidity, fitness and individual preference) with disease-related factors (symptoms from primary tumour, resectability/risks of progression at either site and risk of systemic progression).[10] Thus individual case-management typically comprises a bespoke plan formulated at a multidisciplinary tumour board.[11,12]

Evidence from prospective studies is very limited in this area. Recruitment can be difficult and treatment pathways are complex. The recent METASYNC study took 9 years to accrue 105 patients and as it was based on recruitment from 2006 onwards modern options of neoadjuvant chemo(radio) therapy and the liver-first approach were not evaluated.[13] Current guidelines for management of patients with colorectal cancer and synchronous liver metastases are based largely on retrospective cohort data and systematic reviews.[9,10,14]

This cohort study follows patients with colorectal cancer and liver metastases, from the pathway inception point of case referral to a liver surgery multidisciplinary meeting (tumor board) and provides details on pathway-specific complications and outcomes. CoSMIC is thought to be the first prospective

study directly comparing pathway-specific outcomes in patients with colorectal cancer and synchronous liver metastases treated by a combination of surgery with contemporary systemic chemotherapy with all three modern surgical pathways being utilized.

Methods

Design

The study protocol has been reported in detail previously.[15] Information is reproduced here in sufficient detail to permit appraisal of the study methodology. In overview, CoSMIC is a prospective inception cohort study designed to evaluate the treatment pathways and outcomes of patients with colorectal cancer and synchronous liver-predominant hepatic metastases. An inception cohort study is defined as a study of a group of individuals assembled at a specific and typically early point in their disease pathway. In the case of the CoSMIC study the inception point is that of referral to a multidisciplinary hepatobiliary tumour board (MDT) for consideration for treatment of colorectal cancer with synchronous liver metastases. The study is reported in compliance with the STROBE (strengthening the reporting of observational studies in epidemiology) checklist.[16] (Appendix 1 – online supplemental data).

Setting

The study was set in the regional specialist hepato-pancreato-biliary (HPB) cancer service of the Manchester Royal Infirmary. This is a National Health Service (NHS) regional cancer network-approved centre with a referral population of approximately three million people. Membership of the multi-disciplinary team (MDT) comprised specialist liver surgeons, colorectal surgeons, thoracic surgeons, radiologists, oncologists (including clinical and medical oncologists), histopathologists, cytopathologists and cancer specialist nurses.

Participants

i) Definition of the term "synchronous hepatic metastases" for the purposes of this study.

The term synchronous disease was used if patients had liver metastases either at the point of presentation or had these detected within three months of diagnosis of the primary tumour.

ii) Inclusion/exclusion criteria.

Detailed information on inclusion and exclusion criteria are provided in the published protocol.[15] Key inclusion criteria were adults over 18 years of age, able to give informed consent, with a histological diagnosis of colorectal cancer, no prior history of malignancy and with radiological evidence on either contrast-enhanced CT (computed tomography) or contrast-enhanced MR (magnetic resonance) scan of hepatic metastases at the time of diagnosis of the primary tumour or within 3 months thereof. Patients had a World Health Organization (WHO) performance status of 0, 1 or 2 at enrolment and were considered suitable for chemotherapy.[17] Liver metastases were not biopsied prior to treatment and in addition there was either CT and/or ^{18}fluorodeoxyglucose positron emission tomography ([^{18}F] FDG-PET) evidence of either the absence of extrahepatic metastases or the presence of only small-volume, indeterminate pulmonary lesions.

Between 1st April 2014 and 31st March 2017, 3,084 patient discussions took place at the HPB MDT (See CONSORT flowchart in Figure 1). Of these 599 were new referrals with colorectal hepatic metastases. Two hundred and thirty eight (40%) were patients with colorectal cancer and synchronous liver metastases. After exclusions, 125 patients constitute the final study population.

Data collection

Data were collected on treatment pathways, peri-operative outcomes, timelines for completion of pathway, failure to complete pathway, survival and quality of life. There was a minimum of 12 months outcome information for the entire cohort. Data on race and ethnicity are non-compulsory fields at patient enrolment for clinical care and are therefore not recorded in the study protocol.

Outcomes

i) Overview of treatment pathways

Data are reported on treatment pathway including those patients who were referred for resection but did not undergo surgery. Data are reported on types of surgery undertaken. For bowel surgery, information was recorded on type of resection, laparoscopic or open access, use of primary anastomosis and stoma

rate. Liver surgery was categorized as major or minor resection, single or two-stage hepatectomy and whether or not there was prior modification of the future liver remnant. Use of downsizing chemotherapy, neoadjuvant chemo (radio) therapy, chemotherapy either between interventions or as adjuvant treatment after liver and bowel resection was documented. Response to chemotherapy was assessed by RECIST 1.1 criteria and categorised as complete, partial, stable response or evidence of disease progression.[18]

ii) Peri-operative outcomes

Operative outcomes were categorized by the Dindo-Clavien system of assessment of post-operative morbidity and mortality.[19] For bowel surgery, specific information was collected on anastomotic leak rate and re-operation. The specific post-hepatectomy complications of haemorrhage, bile leak and liver failure were recorded in compliance with the guidance of the International Study Group for Liver Surgery (ISGLS).[20-22] Chemotherapy-related morbidity and mortality were separately recorded.

For all pathways, information was collected on in-patient stay, level of care (ward-based or critical care). Histopathological data were collected including information on complete (R0 – no residual disease) bowel resection and (R0) liver resection.

iii) Timelines for completion of the treatment pathway.

For the purposes of this study, this was defined as the amount of time in months from the initial diagnostic CT to completion of adjuvant chemotherapy, or final surgery if no adjuvant chemotherapy.

iv) Failure to complete the treatment pathway.

For the purposes of this study, the treatment pathway was defined as the programme of surgery and chemo(radio) therapy proscribed at index MDT. Failure was defined as drop-out prior to completion of the allocated treatment sequence and was recorded as the time in months from enrolment.

v) Survival

Overall and disease-free survivals were calculated. Disease-free survival was defined as the absence of tumour on a CT scan of the thorax, abdomen and pelvis undertaken at the completion of the pathway. In the case of those patients with rectal tumours treated by a 'watch and wait' policy, the term disease-free was only applied if there was a combination of radiological, endoscopic and clinical evidence of absence of cancer. Disease progression at end of pathway was assessed by RECIST 1.1 criteria.

vi) *Quality of life.*

Quality of life was assessed using the EuroQol-5-domain, 5-level (EuroQoL-5D-5L) questionnaire and the EORTC (European Organisation for research and treatment of cancer) Quality of Life Core Questionnaire (QLQ C30) together with the EORTC colorectal liver cancer-specific quality of life module (QLQ LM21).[23-24] Assessments were made prior to surgery and between 1 and 2 years after surgery.

Acknowledged Sources of bias[25]

i) Selection bias

Although Manchester Royal Infirmary is the only designated HPB MDT for the network, patients may have been referred out of network. It is not possible to estimate the proportion of study-eligible patients thus referred although it is thought that numbers were small. The inception cohort design means that patients who had started their treatment pathway were excluded and this could result in preferential loss of patients from a particular subgroup. It is also possible that differential interpretation of the clinical

significance of symptoms could preferentially lead to patients with synchronous disease suitable for synchronous surgery presenting outwith the center undergoing bowel-first surgery.

ii) Detection bias

Inadequate baseline staging may have mis-classified patients with extra-hepatic metastases as having liver-limited disease.

iii) Attrition bias

Patients referred for surgery but who were deemed to have unresectable disease at the MDT were referred back to their base centres resulting in preferential loss of data for this group.

iv) Confounding

As this was an inception cohort study, outcomes may have been influenced by a range of factors in addition to treatments provided. Examples include differential clinician preferences or differing clinical competencies which may have confounded outcomes.

Study size

A formal power calculation is not provided for this inception cohort study. Instead, the sample size is informed by the need to provide stable estimates of variance for a range of outcomes and explore the relationship between the treatment pathway and health outcomes.

Statistical analyses

Summary characteristics of patients, treatment and outcomes were reported. Analyses were conducted to a prospectively agreed analysis plan reported in the published protocol.[15] Given the exploratory nature of the analysis and multiplicity of comparisons, a hypothesis generating (rather than testing) framework was applied, where statistical significance (arbitrarily at 5%) was viewed as a marker of

potential interest for further enquiry. Numeric comparisons between groups were compared using one-way analysis of variance; categorical data comparisons used Fisher's exact test. Exploratory analysis of process and clinical outcomes was undertaken to explore the influence of treatment covariates using appropriate regression methods. The primary aim was to contrast survival of patients according to the sequence of care received using Kaplan-Meier survival functions and adjusted for prognostic co-variants using Cox regression. Model building followed a forward stepwise process using variables from patient demographic, primary tumour and liver metastatic characteristics and treatment. Variables were initially identified individually by adding to a base model including age and gender; each model step was tested for significance using the log-likelihood ratio (LLR) test. All analyses were performed in Stata 15.1 (StataCorp LLC, College Station, Texas, USA).

Ethics committee approvals

The study was approved by the NHS Research Ethics Committee North West (Greater Manchester Central) (reference 14/NW/1397).

Study registration

The study was registered with ClinicalTrials.gov (NCT 02456285).

Results

Overview of treatment pathways (Table 1)

i) Demographic profiles and staging information

With respect to sequence of surgery, there was no difference in age, body mass index or Charlson co-morbidity score between groups. However, there was a significant difference in gender between groups with more females in the no-surgery group. All patients underwent a staging CT, with 114 (91%) also undergoing liver MR and 93 (75%) $^{[18F]}$FDG-PET.

ii) Details of patients not undergoing surgery

Patients referred to the MDT for consideration for resection but not undergoing surgery were older and had a higher median Charlson co-morbidity score than those undergoing operative intervention. There was a significant difference between groups in relation to size of largest liver metastasis with a mean (sd) of 5.2 (4.3) cm in the group not undergoing surgery. Two patients whose liver metastatic disease was deemed initially unresectable but were downsized to resectable disease following chemotherapy were subsequently re-allocated into the bowel-first (n=1) and liver-first (n=1) groups respectively.

iii) Modes of presentation

One hundred and six patients (85%) presented with symptoms. All patients with Intestinal obstruction or perforation underwent bowel-first surgery.

iv) Distribution of metastases

The median number of lesions did not differ between surgical pathway groups. Indeterminate thoracic lesions were present in 14 (11%) with the mean size of the largest lesion being 0.5 (0.5 sd) cm.

v) Site of primary tumour and treatment pathway

Left colon tumours were most frequent (n= 69) and were principally allocated to bowel-first (n=44) or synchronous (n=12) pathways. Of 22 patients with right-sided tumours 16 (73%) were allocated to bowel-first surgery.

Operative Pathway detail (Table 2).

i) Colorectal surgery

Of 18 Patients undergoing the liver-first approach, 10 (56%) came to bowel surgery as their second resection. One patient (6%) had a complete response in the primary tumour allowing a watch and wait policy. The liver-first route was the only pathway associated with this policy. Thus, failure to complete pathway due to disease progression after liver resection was seen in 7 (39%) patients who followed the liver-first pathway.

ii) Stoma use

Seventy patients underwent a resection with a primary bowel anastomosis, of whom 20 (29%) had a defunctioning stoma. This was most frequently seen in patients undergoing the liver-first approach.

iii) Liver surgery

Forty patients underwent metastasectomy alone (minor liver resection) (Table 2). The most frequently undertaken major resection was right hepatectomy in 28 (26% of patients undergoing hepatectomy). Twelve patients underwent laparoscopic or laparoscopic-assisted hepatectomy with a conversion rate of 17%.

iv) Liver surgery in relation to bowel surgery.

The liver-first approach was utilised exclusively in patients with left-sided primary tumours. All synchronous procedures were undertaken by open surgery. The most frequently undertaken liver resection as part of a synchronous procedure was metastasectomy alone in 9 (56%) with 6 (40%) undergoing major resections.

v) Use of chemo (radio) therapy within pathways (Table 3)

Neoadjuvant chemotherapy was used in 50 (40% of cohort) for a mean (sd) duration of 4.6 (5.4) months. Mean time from completion of chemotherapy to surgery was 2.6 (1.9) months. The median (range) lines of chemotherapy at neoadjuvant stage was 1(1-2) with oxaliplatin being the most

frequently used chemotherapy backbone drug. Forty nine patients receiving neoadjuvant chemotherapy were re-staged prior to surgery with disease progression being found in 7.

Thirty seven patients had chemotherapy between stages for a median (range) duration of 5.1 (5.2) months. Adjuvant chemotherapy after both surgical steps was used in 54 for a median (range) duration of 5 (4.6) months. KRAS mutation status was tested in 83 patients with 37 having mutant KRAS. Sixty patients were tested for NRAS, all of whom were wild type.

Peri-operative outcomes (Table 4).

i) Post-operative complications after bowel surgery.

There was a significant difference in the highest grade of reported complication between pathways with more higher grade complications in the synchronous pathway. Complications after synchronous surgery include those related to bowel and liver surgery.

ii) Anastomotic leak, re-operation and stoma use after colorectal surgery.

There was no difference in anastomotic leak rate, re-operation or stoma use between synchronous and staged resections.

iii) Complications after liver surgery.

There were no deaths or returns to operating room following liver resection. Bile leak occurred in 9 patients with 3 requiring percutaneous drainage (Grade B).

iv) Synchronous compared to staged surgery.

There was no difference in critical care occupancy or in-patient hospital stay between the staged and synchronous group when both stages of the staged approach are included. The mean total critical care occupancy for staged resections was 5.6 (4.1) days compared to 5.2 (2.9) days for synchronous surgery (t-test; P=0.92). Similarly, the mean total inpatient stay was 16.5 (8.1) days for staged surgery compared to 16.8 (10.3) days for the synchronous group (t-test; P=0.91).

v) Chemotherapy-related complications

There were no grade 3 complications from neoadjuvant chemotherapy. The five most frequent complications in the 50 patients in the neoadjuvant group were peripheral sensory neuropathy in 26 (52%), diarrhoea in 21 (42%), oral mucositis in 20 (40%), constipation in 19 (38%) and nausea in 17 (34%). Constipation rates were significantly different between groups (Fisher's exact test; P=0.004). The same five complications were seen after chemotherapy between stages and also after chemotherapy delivered with adjuvant intent.

Vi) Histopathology

R0 bowel resection status was achieved in 90 (90% of 100 undergoing bowel resectional surgery) and an R0 liver resection was achieved in 62 (66% of 94 undergoing liver resection) with no significant difference between groups for either organ.

Timelines for completion of the treatment pathway (Table 5)

There was no significant difference in the time taken to complete treatment between the three pathways. Twenty-one (19% of patients starting surgical pathways) failed to complete. Failure to complete pathway rate was greatest (7 [39%]) for patients undergoing the liver-first approach (Chi-square, P=0.041) with all being due to disease progression before the second stage. Thirteen patients failed to complete the bowel-first pathway (1 patient progressed during neoadjuvant chemotherapy, 9 patients progressed between staged surgeries and 3 patients failed liver resection (non-therapeutic laparotomy). One patient (6%) failed to complete the synchronous surgery pathway due to inoperable disease at first laparotomy.

Fifty eight (54%) were disease-free at the end of the pathway with no significant difference between groups (Chi-square, P=0.970). Thirty six (35%) were disease-free at 12 months with no significant difference between groups (Chi-square, P=0.448)

Survival Analysis

The Kaplan-Meier survival curve for the cohort is seen in Figure 2a and staged versus synchronous in Figure 2b. A base case Cox regression model using age and gender as covariates showed progressively lower survival for older patients and for patients of female sex. From a panel of demographic, treatment and disease variables two covariates were identified which improved the base model: the size of the largest liver lesion and the sequence of surgery. The sequence of surgery was added to the base model resulting in an improved model (chi^2 (df=3) = 31.24, $p<0.001$). The largest liver lesion size (as a continuous variable) was added to this expanded model but did not provide further improvement (chi^2 (df=1) = 1.09, p=0.2976). Thus, a simple model of age, gender and treatment pathway provided the best model for the CoSMIC inception cohort (Appendix 2 in online supplemental data). Survival is statistically similar between surgical groups, although absolute numbers are not large enough to discern smaller differences.

Quality of life

The EuroQol (EQ-5D-5L) and EORTC Quality of Life Core Questionnaire (QLQ C30) scores are shown in Appendix 3 (online supplement). EORTC colorectal liver cancer-specific quality of life module (QLQ LM21) scores are shown in Appendix 4 (online supplement). Complete quality of life questionnaires were recorded for 61 patients prior to surgery and for 36 patients between 1 and 2 years after surgery. Overall, quality of life scores were similar before and after surgery.

DISCUSSION

CoSMIC is thought to be the first prospective study directly comparing pathway-specific outcomes in patients with colorectal cancer and synchronous liver metastases, with all three surgical sequences being available together with contemporary systemic chemo(radio)therapy and starting from the point of referral for specialist liver surgery.

There are important study limitations. First, this was a small study population, albeit, by the nature of potentially resectable liver metastatic colon cancer, a highly focused cohort, and, unlike other studies in the literature, collected over a short period of time with consistent chemotherapy regimens. There is therefore a relatively small number of patients undergoing liver-first and synchronous resections in this homogenous patient group. Second, from an international perspective, the results reflect practice within the UK's NHS and it is acknowledged that tertiary liver surgery referral practices vary between healthcare systems.[26-29]

The focus of much current controversy is on the management of patients with colorectal cancer and potentially resectable liver metastases – this is the cohort of the CoSMIC study.[30-33]

Avoiding over-interpretation of these data, several points emerge. First, the study confirms that even in this selected referral population, those who do not or cannot undergo surgery, typically because of a combination of age, co-morbidity and tumor size have a less favourable outcome.

In terms of pathway, patients with obstructing or perforated cancers were preferentially treated by the bowel-first pathway. The liver-first pathway was preferentially selected for patients with left-sided and rectal tumours, in particular those undergoing chemoradiotherapy. All synchronous surgery was undertaken by open surgery and was associated with a higher grade of peri-operative complications compared to staged pathways but sub-group numbers are small. Although the liver-first pathway was the only one associated with the option of avoidance of rectal surgery this pathway also carried the highest rate of failure to progress to second stage surgery because of disease progression between stages.

A key finding of CoSMIC is that in oncologic and health-care occupancy terms equipoise exists between all three pathways. This finding from a prospective dataset mirrors evidence gleaned from systematic reviews and retrospective cohort data and suggests that in current practice there is neither a requirement for nor a realistic prospect of clinician/patient support for randomized comparisons of staged versus synchronous surgery as these options confer similar outcomes.[34-37] CoSMIC does suggest that the patient experience may vary between pathways and this requires further investigation, together with assessment of the criteria for optimal pathway allocation.

The data from CoSMIC confirm that modern chemo(radio)therapy can be integrated into treatment pathways. The practical delay between presentation and surgery for patients receiving neoadjuvant chemotherapy was in the order of 6 months. If chemotherapy is used between stages, CoSMIC shows the importance of formal re-staging prior to proceeding to second-stage surgery. Although there was no difference in pathway times between groups, CoSMIC clearly demonstrates that current treatment pathways are both complex and lengthy.[38,39] The evidence for the liver-first approach in particular could be further evaluated.[40-42]

This study pre-dates the clinical impact of the consensus molecular sub-types of colon cancer and the increasing information base about the genetic heterogeneity of metastatic colon cancer.[43-46] Such information is likely to fundamentally alter the management of this patient cohort. Current knowledge of the mutational burden of colorectal cancer influences choice of chemotherapy but is yet to impact meaningfully on surgical decision making.[47-49]

Better understanding of this cancer biology may influence a direction towards more systemic treatment, even in patients with apparently 'easy-to-resect' liver metastases and primary tumours. The recently reported RAPIDO study in patients with rectal cancer confirms that systemic chemotherapy delivered prior to surgery confers benefit.[50] The role of surgery remains important as shown by the survival outcomes in patients undergoing resection.

In conclusion, the CosMIC study has undertaken the first prospective cohort evaluation of pathway-specific outcomes for patients with colorectal cancer and synchronous liver metastases. The findings show that those who cannot undergo surgery have poorer outcomes. Of patients undergoing resection, all three pathways produce similar outcomes although the liver-first approach was associated with the highest rate of failure to complete stages. Better understanding of the genetic basis of metastatic colon cancer and, equally importantly an appreciation of and consideration of the patient's views on treatment are likely to guide future management of this challenging clinical condition.

ACKNOWLEDGEMENT.

We dedicate this study to the memory of Lolita Chan.

COLLABORATORS

Aali J Sheen MD FRCS[1,2,3], Derek A O'Reilly PhD FRCS[1,2], Saurabh Jamdar MD FRCS[1,2], Rahul Deshpande MS FRCS[1], Nicola de Liguori Carino FRCS[1], Thomas Satyadas MS FRCS[1], Saifee Mullamitha MD MRCP[4], Michael Braun MRCP PhD[4], Nooreen Alam MRCP FRCR[4], Jurjees Hassan MSc MD FRCP[4], Gregory Wilson DRCOG FRCP Dip Onc[4], Raj Rajashankar MRCP FRCR[5], Santhalingam Jegatheeswaran FRCS[1], Minas Baltatzis PhD[1], Professor Ray McMahon MD FRCPath[6], Rishi Sethi MRCS FRCR[5], James Hill ChM FRCS[7], David Smith BSc FRCS[8], Christopher Smart FRCS[9], Arif Khan MS FRCS[10], Mohammud Kurrimboccus MD FRCS[11], Jonathan Epstein MD FRCS[12], Fergus Reid FRCS[13], Kamran Siddiqui FRCS[14], Ramesh Aswatha MD FRCS[15] and Marius Paraoan MD FRCS[16].

[1]Hepatobiliary Unit, Manchester Royal Infirmary, [2]Faculty of Medicine, University of Manchester, [3]Manchester Metropolitan University, [4]Oncology Service, Christie Hospital, Manchester, [5]Department of Radiology, Manchester Royal Infirmary, [6]Department of Histopathology, Manchester Royal Infirmary, [7]Colorectal Surgery Unit, Manchester Royal Infirmary, [8]Department of Surgery, Royal Bolton Hospital, [9]Department of Surgery, Macclesfield District General Hospital, [10]Department of Surgery, Leighton Hospital, Crewe, [11]Department of Surgery, North Manchester General Hospital, [12]Department of Surgery, Salford Royal Hospital, [13]Department of Surgery, Stepping Hill Hospital, [14]Department of Surgery, Tameside General Hospital, [15]Department of Surgery, Wythenshawe Hospital, [16]Department of Surgery, Royal Albert Edward Infirmary.

REFERENCES

1. Siriwardena AK, Mason JM, Mullamitha S, Hancock HC, Jegatheeswaran S. Management of colorectal cancer presenting with synchronous liver metastases. *Nat Rev Clin Oncol* 2014;11:446-59.
2. Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M et al. Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986; 150: 195 – 203.
3. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy P. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg* 2006;**93**, 465-74.
4. Adam R, de Gramont A, Figueras J et al. Managing synchronous liver metastases from colorectal cancer:A multidisciplinary international consensus. *Cancer Treat Rev* 2015; 41:729–41.
5. Adam R, De Gramont A, Figueras J et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012;17):1225-39.
6. Jegatheeswaran S, Mason JM, Hancock HC, Siriwardena AK. The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: a systematic review. *JAMA Surg* 2013;148:385-91.
7. Conci S, Ruzzenente A, Pedrazzani C et al. Simultaneous approach for patients with synchronous colon and rectal liver metastases: Impact of site of primary on postoperative and oncological outcomes. *Eur J Surg Oncol*. 2020;25:S0748-7983.
8. Chen X, Hu W, Huang C et al. Survival outcome of palliative primary tumor resection for colorectal cancer patients with synchronous liver and/or lung metastases: A retrospective

cohort study in the SEER database by propensity score matching analysis. *Int J Surg* 2020;80:135-52.

9. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer. Version 2.2016. www.nccn.org (accessed 21st January 2021).
10. Schmoll HJ, Van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol* 2012; 23: 2479–16.
11. Ignatavicius P, Oberkofler CE, Chapman WC et al. Choices of Therapeutic Strategies for Colorectal Liver Metastases Among Expert Liver Surgeons: A Throw of the Dice? *Ann Surg* 2020;272:715-22.
12. Jones RP, Kokudo N, Folprecht G et al. Colorectal Liver Metastases: A Critical Review of State of the Art. Liver Cancer 2016;6:66-71.
13. Boudjema K, Locher C, Sabbagh C et al. Simultaneous Versus Delayed Resection for Initially Resectable Synchronous Colorectal Cancer Liver Metastases: A Prospective, Open-label, Randomized, Controlled Trial. *Ann Surg* 2021;273:49-56.
14. Baltatzis M, Chan AK, Jegatheeswaran S, Mason JM, Siriwardena AK. Colorectal cancer with synchronous hepatic metastases: Systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. *Eur J Surg Oncol* 2016;42:159-65.
15. Siriwardena AK, Chan AKC, Ignatowicz AM, Mason JM. Colorectal cancer with Synchronous liver-limited Metastases: the protocol of an Inception Cohort study (CoSMIC). *BMJ Open* 2017;7(6):e015018.
16. STROBE statement. (strengthening the reporting of observational studies in epidemiology) checklist. www.strobe-statement.org (accessed 14th April 2014).
17. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.

18. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours:Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228 – 47.
19. Dindo D, Desmartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13.
20. Rahbari N, Garden OJ, Padbury R et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *HPB (Oxford)* 2011;13:528-35.
21. Brooke-Smith M, Figueras J, Ullah S et al. Prospective evaluation of the International Study Group for Liver Surgery definition of bile leak after a liver resection and the role of routine operative drainage: an international multicentre study. *HPB (Oxford)* 2015;17:46-51.
22. Sultana A, Brooke-Smith M, Ullah S et al. Prospective evaluation of the International Study Group for Liver Surgery definition of post hepatectomy liver failure after liver resection: an international multicentre study. *HPB (Oxford)* 2018;20:462-69.
23. Eq-5D-5L user guide. Basic information on how to use the EQ-5D-5L instrument. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf
24. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Nat Cancer Inst* 1993; 85: 365-76.
25. Higgins JPT, Altman DG, Gøtzsche PC et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
26. Padmanabhan C, Nussbaum DP, D'Angelica M. Surgical Management of Colorectal Cancer Liver Metastases. *Surg Oncol Clin N Am* 2021;30:1-25.
27. Reding D, Pestalozzi BC, Breitenstein S et al. Treatment strategies and outcome of surgery for synchronous colorectal liver metastases. *Swiss Med Wkly* 2017;147:w14486.

28. Lang H, Baumgart J, Heinrich S et al. Extended Molecular Profiling Improves Stratification and Prediction of Survival After Resection of Colorectal Liver Metastases. *Ann Surg* 2019;270:799-805.

29. Allard M-A, Nishioka Y, Beghdadi N et al. Multicentre study of perioperative versus adjuvant chemotherapy for resectable colorectal liver metastases. *BJS Open* 2019;3:678-86.

30. Imai K, Adam R, Baba H. How to increase the resectability of initially unresectable colorectal liver metastases: A surgical perspective. *Ann Gastroenterol Surg* 2019;3:476-86.

31. Nakajima K, Takahashi S, Saito N et al. Efficacy of the predicted operation time (POT) strategy for synchronous colorectal liver metastasis (SCLM): feasibility study for staged resection in patients with a long POT. *J Gastrointest Surg* 2013;17:688-95.

32. Schlag P, Hohenberger P, Herfarth C. Resection of liver metastases in colorectal cancer--competitive analysis of treatment results in synchronous versus metachronous metastases. *Eur J Surg Oncol* 1990;16:360-65.

33. Datta J, Narayan RR, Goldman DA et al. Distinct Genomic Profiles are Associated With Conversion to Resection and Survival in Patients With Initially Unresectable Colorectal Liver Metastases Treated With Systemic and Hepatic Artery Chemotherapy. *Ann Surg* 2020;doi: 10.1097/SLA.0000000000004613.

34. Thelen A, Jonas S, Benckert C et al. Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer. *Int J Colorectal Dis* 2007;22:1269-76.

35. Martin RCG, Augenstein V, Reuter NP et al. Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. *J Am Coll Surg* 2009;208:842-50.

36. Li Z-Q, Liu K, Duan J-C et al. Meta-analysis of simultaneous versus staged resection for synchronous colorectal liver metastases. *Hepatol Res* 2013;43:72-83.

37. Bogach J, Wang J, Griffiths C et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cohort study. *Int J Surg* 2020;74:68-75.

38. Wang J, Griffiths C, Simunovic M et al. Simultaneous versus staged resection for synchronous colorectal liver metastases: A population-based cost analysis in Ontario, Canada - Health economic evaluation. *Int J Surg* 2020;78:75-82.

39. Abbott DE, Cantor SB, Hu C-Y et al. Optimizing clinical and economic outcomes of surgical therapy for patients with colorectal cancer and synchronous liver metastases. *J Am Coll Surg* 2012;215:262-70.

40. Andres A, Toso C, Adam R et al. A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. *Ann Surg* 2012;256:772-78.

41. de Jong, MC, Beckers RCJ, van Woerden V et al. The liver-first approach for synchronous colorectal liver metastases: more than a decade of experience in a single centre. *HPB (Oxford)* 2018;20:631-40.

42. Ihnát P,Vávra P, Zonča P. Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go? *World J Gastroenterol* 2015;21:7014-21.

43. Guinney J, Dienstmann R, Wang X et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21,1350–56.

44. Dienstmann R, Vermeulen L, Guinney J et al. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. *Nat Rev Cancer*. 2017;17:79-92.

45. Lal N, White BS, Goussous G et al. KRAS Mutation and Consensus Molecular Subtypes 2 and 3 Are Independently Associated with Reduced Immune Infiltration and Reactivity in Colorectal Cancer. *Clin Cancer Res* 2018;24:224-33.

46. Pitroda SP, Khodarev NN, Huang L et al. Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. *Nat Commun* 2018;9:1793.doi: 10.1038/s41467-018-04278-6.

47. Dolatkhah R, Dastgiri S, Sadat ATS et al. Impact of RAS/RAF mutations on clinical and prognostic outcomes in metastatic colorectal cancer. *Bioimpacts* 2021;11:5-14.

48. Formica V, Lucchetti J, Doldo E et al. Clinical Utility of Plasma KRAS, NRAS and BRAF Mutational Analysis with Real Time PCR in Metastatic Colorectal Cancer Patients-The Importance of Tissue/Plasma Discordant Cases. *J Clin Med* 2020;10(1):87. doi:10.3390/jcm10010087.

49. Gürsoy P, Çakar B, Almuradova E et al. The effectiveness of cetuximab and panitumumab when combined with FOLFIRI in second-line treatment of KRAS wild type metastatic colorectal cancers. Single centre experience. *J Chemother* 2020:21;1-7.

50. Bahadoer RR, Dijkstra EA, van Etten B et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:29-42.

Table 1: Patient demographics and details of disease distribution.

	All Cohort	Liver First	Bowel First	Synchronous	No Surgery	*p-value*
n	125	18	75	16	16	
Patient Demographics						
Age, median (range) years	66.5 (30.8 - 85.6)	65.9 (45.9 - 84.1)	65.7 (30.8 - 85.6)	69.3 (54.5 - 80.6)	72.4 (44.1 - 82.4)	*0.351*
Sex, male (%)	80 (64%)	12 (67%)	54 (72%)	8 (50%)	6 (38%)	*0.042**
BMI, mean (SD), kg/m^2	27.3 (5.9)	26.2 (4.8)	27.2 (5.4)	28.4 (7.2)	28.8 (8.9)	*0.419*
Charlson Score (median)	9 (6 - 14)	9 (7 - 11)	9 (6 - 12)	10 (8 - 11)	10 (7 - 14)	*0.308*
Presentation*						
Asymptomatic Diagnosis	19 (15%)	1 (6%)	11 (15%)	5 (31%)	2 (12%)	
Symptomatic Presentation	106 (85%)	17 (94%)	64 (85%)	11 (69%)	14 (88%)	
Intestinal Obstruction	15 (12%)	0 (0%)	15 (20%)	0 (0%)	0 (0%)	
Perforation / Peritonitis	3 (2%)	0 (0%)	3 (4%)	0 (0%)	0 (0%)	
Primary Colorectal Cancer Location*						
Right Colon	22 (18%)	0 (0%)	16 (21%)	4 (25%)	2 (12%)	
Left Colon	69 (55%)	5 (28%)	44 (59%)	12 (75%)	8 (50%)	
Rectum	34 (27%)	13 (72%)	15 (20%)	0 (0%)	6 (38%)	
Liver Metastases						
Unilobar Distribution*	75 (60%)	10 (56%)	44 (59%)	10 (63%)	11 (69%)	*0.089*
Right (% of unilobar distribution)**	58 (77%)	10 (100%)	34 (77%)	8 (80%)	6 (55%)	
Median (range) Number of Lesions	2 (1 - 20)	2 (1 - 7)	2 (1 - 20)	1.5 (1 - 11)	1.5 (1 - 12)	*0.428*
Size of Largest Lesion, cm (SD)	3.3 (2.7)	3.2 (2.0)	2.8 (2.3)	3.7 (3.1)	5.2 (4.3)	*0.018**
Thoracic Metastases						
Indeterminant Thoracic Lesions	14 (11%)	4 (22%)	6 (8%)	4 (25%)	0 (0%)	*0.039**
Bilateral	11 (79%)	3 (75%)	5 (83%)	3 (75%)	-	*0.039**
Number of Lesions, Median (range)	1.4 (1.0-5.0)	1.2 (1.0-2.0)	1.2 (1.0-2.0)	2.0 (1.0-5.0)	-	*0.628*
Size of largest lesion, cm (SD)	0.5 (0.5)	0.4 (0.4)	0.8 (0.8)	0.5 (0.5)	-	*0.628*

Table 2. Operative Details of Bowel Surgery

	All Surgical Patients	Liver First	Bowel First	Synchronous
n	**109**	**18**	**75**	**16**
Right Colon Resection	27 (25%)	0 (0%)	22 (29%)	5 (31%)
Left Colon Resection	10 (9%)	0 (0%)	7 (9%)	3 (19%)
Hartmann's Procedure	14 (13%)	0 (0%)	10 (13%)	4 (25%)
Anterior Resection	39 (36%)	8 (44%)	28 (37%)	3 (19%)
Abdominoperineal Resection	6 (6%)	2 (11%)	4 (5%)	0 (0%)
Subtotal Colectomy	3 (3%)	0 (0%)	3 (4%)	0 (0%)
Local / Wedge Resection	1 (1%)	0 (0%)	0 (0%)	1 (6%)
No Surgery (Complete Response)	1 (1%)	1 (6%)	0 (0%)	0 (0%)
Incomplete pathway – failed to progress to second stage.	8 (7%)	7 (39%)	1 (1%)	0 (0%)
Modality*				
Open	67 (67%)	6 (60%)	45 (61%)	16 (100%)
Laparoscopic	27 (27%)	4 (40%)	23 (31%)	0 (0%)
Laparoscopic assisted	2 (2%)	0 (0%)	2 (3%)	0 (0%)
Laparoscopic converted to Open	4 (4%)	0 (0%)	4 (5%)	0 (0%)
Primary Anastomosis, n (%)**	70 (88%)	6 (75%)	52 (87%)	12 (100%)
Defunctioning Stoma, n (%)†	20 (29%)	5 (83%)	11 (21%)	4 (33%)

Table 2 (continued). Operative Details of Liver Surgery

	All Surgical Patients	Liver First	Bowel First	Synchronous
n	**109**	**18**	**75**	**16**
Right Hepatectomy	28 (26%)	4 (22%)	22 (29%)	2 (13%)
Right Anterior Sectionectomy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Right Posterior Sectionectomy	7 (6%)	2 (11%)	4 (5%)	1 (6%)
Right Trisectionectomy	3 (3%)	1 (6%)	1 (1%)	1 (6%)
Left Trisectionectomy	3 (3%)	1 (6%)	2 (3%)	0 (0%)
Left Hepatectomy	4 (4%)	0 (0%)	4 (5%)	0 (0%)
Left Lateral Sectionectomy	7 (6%)	0 (0%)	5 (7%)	2 (13%)
Isolated Caudate Resection	2 (2%)	1 (6%)	1 (1%)	0 (0%)
Metastasectomy alone.	40 (37%)	9 (50%)	22 (29%)	9 (56%)
Metastasectomy (in addition to an anatomical resection)*	32 (59%)	7 (78%)	21 (54%)	4 (67%)
*One Segment***	14 (44%)	3 (43%)	8 (38%)	3 (75%)
*Two Segments***	10 (31%)	1 (14%)	8 (38%)	1 (25%)
*Three Segments***	8 (25%)	3 (43%)	5 (24%)	0 (0%)
*Four or More Segments***	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Inoperable at time of resection	3 (3%)	0 (0%)	2 (3%)	1 (6%)
Incomplete pathway, failed to progress to second stage.	10 (9%)	0 (0%)	10 (13%)	0 (0%)
No Surgery (Complete Response)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
No Surgery (Radiofrequency Ablation)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Modality†				
Open	85 (88%)	18 (100%)	51 (81%)	16 (100%)
Laparoscopic	9 (9%)	0 (0%)	9 (14%)	0 (0%)
Laparoscopic assisted	1 (1%)	0 (0%)	1 (2%)	0 (0%)
Laparoscopic converted to Open	2 (2%)	0 (0%)	2 (3%)	0 (0%)
Major Resection (>3 segments)††	54 (57%)	11 (61%)	37 (61%)	6 (40%)
Planned Two-Stage Resection	3 (3%)	0 (0%)	2 (3%)	1 (7%)
Preoperative Portal Vein Embolization	4 (4%)	1 (6%)	2 (3%)	1 (6%)

Table 3. Chemo(radio)therapy Details

	All Surgical Patients	Liver First	Bowel First	Synchronous
n	**109**	**18**	**75**	**16**
Neoadjuvant Long Course Chemoradiotherapy	**11**	**7**	**4**	**0**
Neoadjuvant Short Course Radiotherapy	**9**	**2**	**7**	**0**
Neoadjuvant Chemotherapy	**50**	**16**	**28**	**6**
Duration, mean months (SD)	4.6 (5.4)	4.3 (5.8)	4.9 (5.8)	4.2 (2.5)
Time from finishing neoadjuvant chemotherapy to Surgery, mean months (SD)	2.6 (1.9)	3.1 (1.3)	2.4 (2.4)	2.3 (0.5)
Lines of Chemotherapy, median (range)	1 (1 - 2)	1 (1 - 1)	1 (1 - 2)	1 (1 - 2)
Single Agent 5-FU	7	3	4	0
IrMdG	17	6	10	1
OxMdG	28	7	16	5
+ Bevacizumab	2	1	1	0
+ Cetuximab	10	3	6	1
+ Panitumumab	2	0	1	1
Restaged (RECIST) prior to Surgery	49	16	27	6
Complete Response	1	0	1	0
Partial Response	32	10	18	4
Stable Disease	8	4	3	1
Progressive Disease	7	2	5	0
Chemotherapy between stages	**37**	**6**	**31**	-
Duration, mean months (SD)	5.1 (5.2)	3.6 (4.2)	5.3 (5.4)	-
Time from finishing chemotherapy to Stage 2 Surgery, mean months (SD)	3.5 (3.0)	2	3.5 (3.1)	-
Lines of Chemotherapy, median (range)	1 (1 - 3)	1 (1 - 2)	1 (1 - 3)	-
Single Agent 5-FU	6	2	4	-
IrMdG	11	3	8	-
OxMdG	25	2	23	-
+ Bevacizumab	1	0	1	-
+ Cetuximab	1	1	0	-
+ Panitumumab	1	0	1	-
+ Aflibercept	1	0	1	-
+ Raltitrexed	1	0	1	-
Restaged (RECIST) prior to 2nd Stage Surgery	46	11	35	-
Complete Response	3	1	2	-
Partial Response	11	0	11	-
Stable Disease	10	2	8	-
Progressive Disease	22	8	14	-
Adjuvant Chemotherapy	**54**	**5**	**39**	**10**
Adjuvant Chemotherapy Duration, months (range)	5.0 (4.6)	4.1 (2.6)	4.7 (5.0)	6.3 (3.7)
Lines of Chemotherapy, median (range)	1 (1 - 2)	1 (1 - 1)	1 (1 - 2)	1 (1 - 1)
Single Agent 5-FU	19	1	16	2
IrMdG	12	1	7	4
OxMdG	27	4	17	6
+ Bevacizumab	2	0	2	0
+ Cetuximab	2	0	1	1
+ Aflibercept	1	0	1	0
+ Raltitrexed	2	0	1	1

Table 4. Perioperative Outcomes

	All Surgical Patients	Liver First	Bowel First	Synchronous	*p-value*
n	**109**	**18**	**75**	**16**	
Bowel Surgery Postoperative Outcomes					
Postoperative Complications (CD)					*0.003**
Grade I	50 (64%)	8 (89%)	38 (72%)	4 (25%)	
Grade II	20 (26%)	0 (0%)	12 (23%)	8 (50%)	
Grade IIIA	5 (6%)	1 (11%)	1 (2%)	3 (19%)	
Grade IIIB	2 (3%)	0 (0%)	2 (4%)	0 (0%)	
Grade IV	1 (1%)	0 (0%)	0 (0%)	1 (6%)	
Grade V	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Anastomotic Leak Rate	2 (4.3%)	1 (17%)	1 (2%)	0 (0%)	*0.990*
Re-operation	3 (3.4%)	0 (0%)	2 (3%)	1 (6%)	
Length of Critical Care Stay, days (SD)	2.8 (3.7)	1.9 (1.6)	2.0 (3.8)	5.2 (2.9)	*<0.001**
Length of Hospital Stay, days (SD)	10.6 (7.9)	10.9 (7.5)	8.7 (6.2)	16.8 (10.3)	*0.002**
Readmission within 30 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Bowel Resection Margin					
R0	90 (90%)	8 (80%)	67 (91%)	15 (94%)	*0.855*
R1	9 (9%)	2 (20%)	6 (8%)	1 (6%)	
R2	1 (1%)	0 (0%)	1 (1%)	0 (0%)	
Missing data	*22*	*1*	*21*	*0*	
Liver Surgery / Synchronous Surgery Postoperative Outcomes					
Postoperative Complications (CD)					*0.003**
Grade I	53 (56%)	8 (47%)	42 (68%)	4 (25%)	
Grade II	28 (30%)	4 (24%)	16 (26%)	8 (50%)	
Grade IIIA	11 (12%)	5 (29%)	3 (5%)	3 (19%)	
Grade IIIB	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade IV	2 (2%)	0 (0%)	0 (0%)	1 (6%)	
Grade V	0 (0%)	0 (0%)	1 (2%)	0 (0%)	
Liver Failure	2 (2%)	1 (6%)	1 (2%)	0 (0%)	*0.984*
Bile Leak (ISGLS Grading)					*0.802*
Grade A	6 (7%)	0 (0.0%)	5 (8%)	1 (6%)	
Grade B	3 (3%)	2 (12%)	1 (2%)	0 (0%)	
Grade C	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Re-operation	0 (0%)	0 (0%)	0 (0%)	1 (6%)	
Length of Critical Care Stay, days (SD)	3.9 (2.3)	4.1 (2.5)	3.4 (1.9)	5.2 (2.9)	*0.061*
Length of Hospital Stay, days (SD)	9.4 (6.8)	10.1 (5.9)	7.4 (4.5)	16.8 (10.3)	*0.005**
Readmission within 30 days	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Liver Resection Margin					
R0	62 (66%)	12 (67%)	39 (64%)	11 (73%)	*0.505**
R1	32 (34%)	6 (33%)	22 (36%)	4 (27%)	

Table 5: Pathway Completion.

	All Surgical Patients	Liver First	Bowel First	Synchronous	*p-value*
n	109	18	75	16	
Total Pathway Time, mean months (SD)*	13.5 (8.1)	15.2 (8.9)	13.6 (8.9)	11.6 (4.8)	0.535
Failed Pathway (%)	21 (19%)	7 (39%)	13 (17%)	1 (6%)	0.041
Disease progression between surgery	17 (81%)	7 (100%)	10 (77%)	-	
Inoperable disease at first surgery	1 (5%)	-	-	1 (100%)	
Inoperable disease at second stage surgery	2 (10%)	-	2 (15%)	-	
Failed two-stage liver surgery	1 (5%)	-	1 (8%)	-	
Disease-free at end of Pathway (%)	58 (53%)	9 (50%)	40 (53%)	9 (56%)	0.970
Disease-Free at 12 months (%)	36 (32%)	4 (22%)	27 (36%)	5 (31%)	0.448

Figure 1. CoSMIC CONSORT Diagram

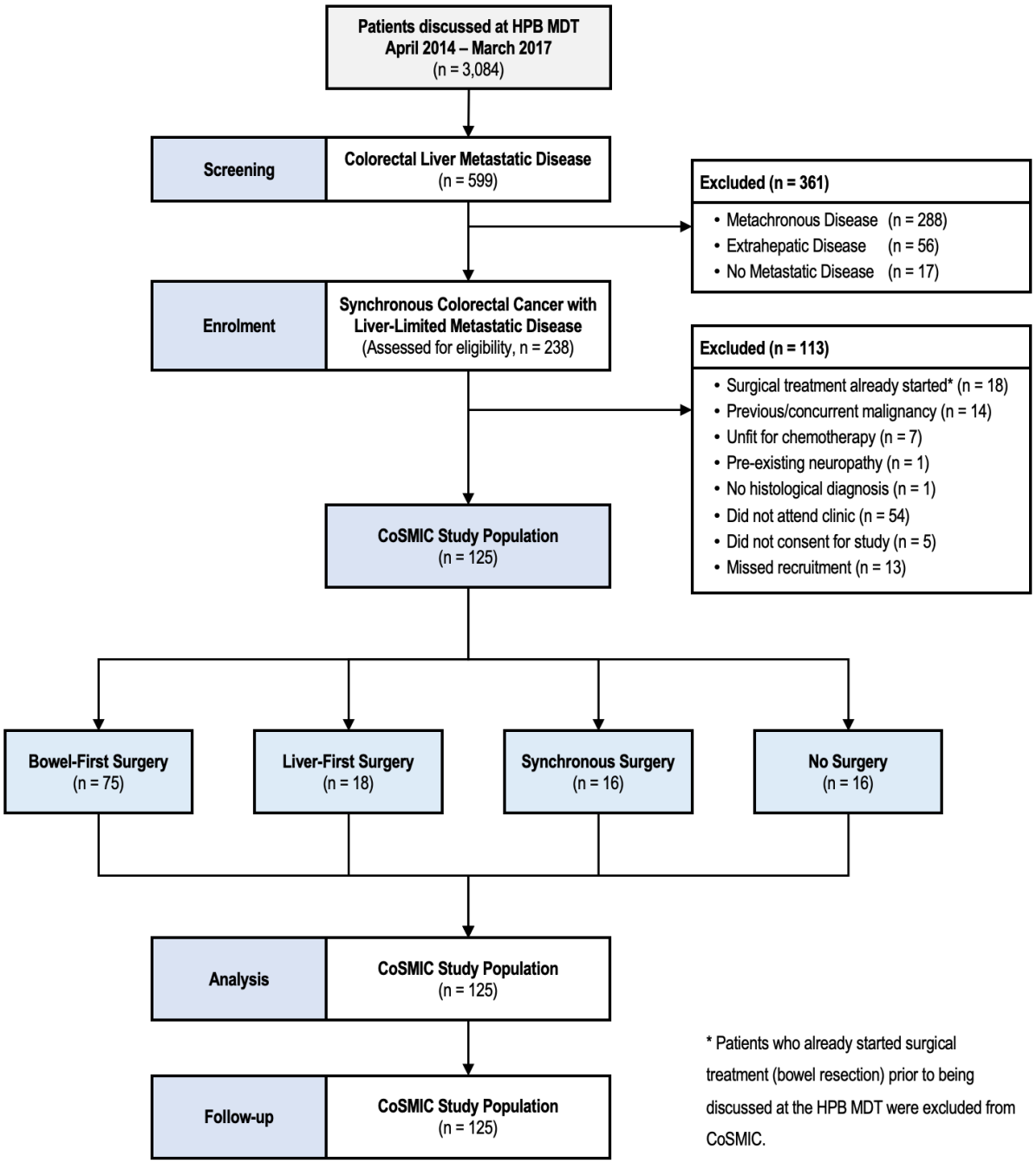

Figure 2. Kaplan-Meier curve of overall survival by sequence of surgery

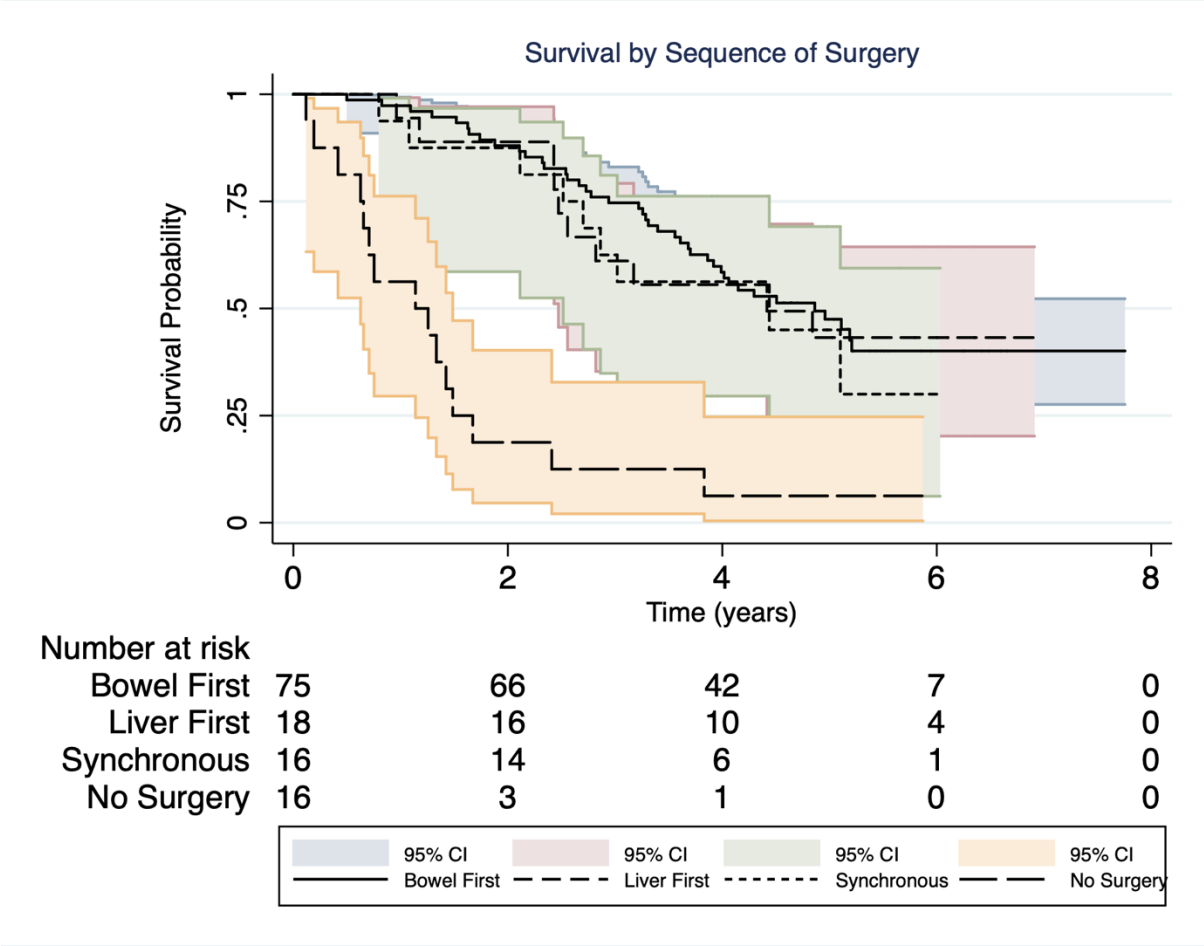

Figure 3. Kaplan-Meier curve of overall survival: staged vs synchronous Surgery

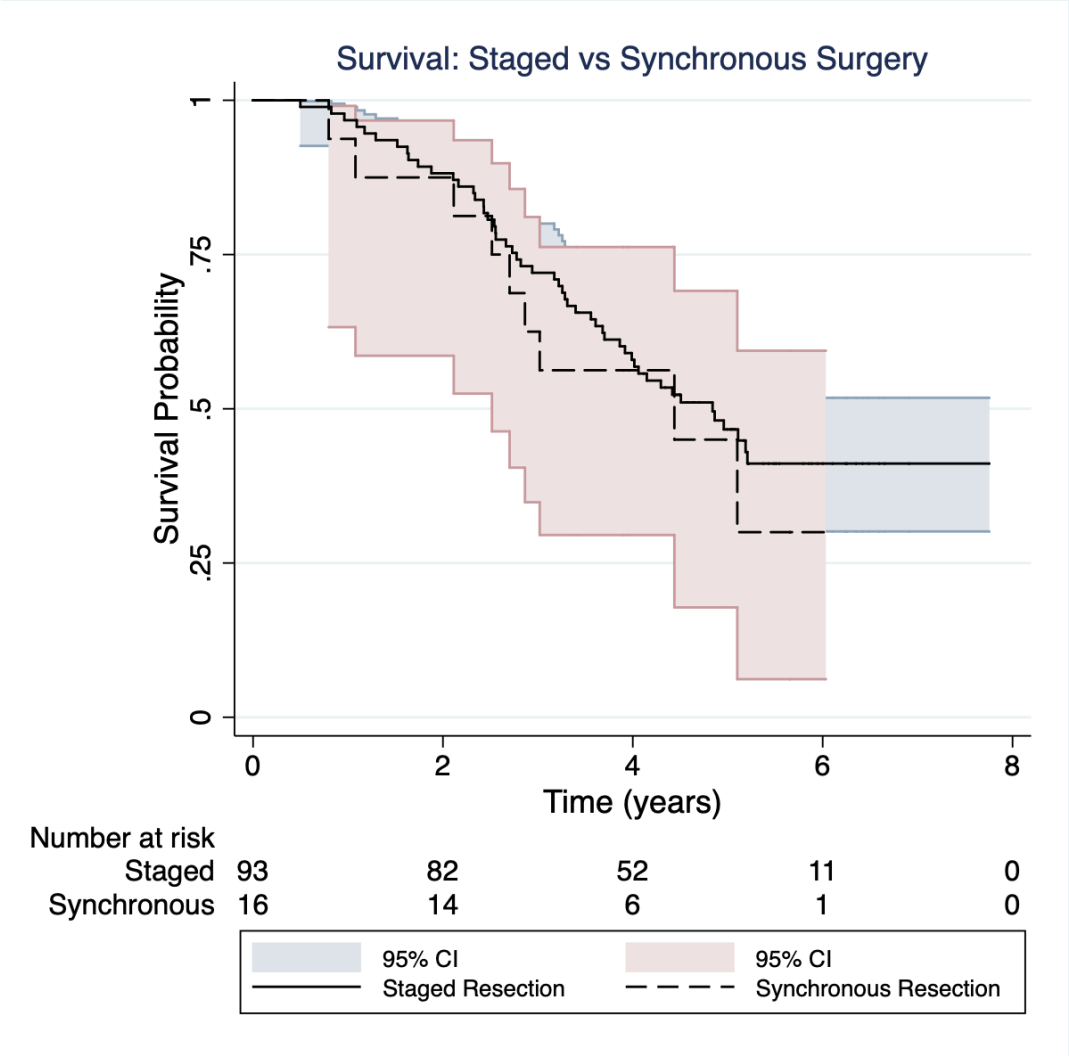

Table and figure legends.

Table 1: Patient demographics and details of disease distribution.

BMI = Body Mass Index. *denominator for percentages refers to individual clinical pathway. Right = right lobe disease**

Table 2: Operative details of bowel and liver surgery

In relation to bowel Surgery: Denominator for percentages refers to treatment pathway unless otherwise stated. *Denominator refers to the number of patients who underwent surgery per pathway. **Primary anastomosis as a percentage of patients who underwent a colorectal resection where an anastomosis could have been formed. †Denominator as a percentage of patients who underwent a primary anastomosis.

In relation to liver surgery: Segments refer to Couinaud's segments. *Denominator refers to patients who underwent an anatomical liver resection. ** Denominator refers to patients undergoing metastasectomy in addition to anatomical liver resection.

†Denominator for percentages refers to the number of patients who underwent surgery per pathway (including those that were inoperable at laparotomy). ††Denominator for percentages refers to patients who underwent the intended resection.

Table 3 Chemo(radio) therapy details.

5-FU: 5-fluouracil. IrMdG: Irinotecan modified de Gramont. OxMdG: Oxaliplatin modified de Gramont. RECIST: Response Evaluation Criteria in Solid Tumours.

Table 4: Peri-operative outcomes

CD = Clavien-Dindo. ISGLS = International Study Group for Liver Surgery. Peri-operative complications in the synchronous group are presented in relation to both bowel and liver surgery. For patients undergoing synchronous surgery, critical care and in-patient stay are duplicated and seen in parallel to each component of the staged procedures.

Table 5:Pathway completion

*Patients who failed the pathway were not included in the total pathway time.

Figure 1: CONSORT flowchart.

HPB MDT = Hepato-Pancreato-Biliary Multidisciplinary team meetings. Eighteen patients with an initial diagnosis of colorectal cancer and synchronous liver metastases who had undergone surgery and/or other treatments and were substantially along their treatment pathway were not recruited.

Figure 2a: Kaplan-Meier overall survival curve by sequence of surgery.

Figure 2b: Kaplan-Meier overall survival curve: staged versus synchronous surgery.

Legend for Appendix 2: Online supplemental data. Cox regression model for the CoSMIC cohort

HR, Hazard Ratio; SE, Standard Error; CI 95% Confidence Interval; LL, Log Likelihood; LLR, Log Likelihood Ratio; df, degrees of freedom

Appendix 1 (online supplemental data) – STROBE Checklist

	Item	Recommendation
Title and abstract	1	(a) CoSMIC: Colorectal Cancer and Synchronous Liver-Limited Metastases: An Inception Cohort (b) CoSMIC provides a first mixed method approach to study the process of care and outcomes following synchronous or staged surgery in patients with colorectal cancer and synchronous liver-limited metastases. CoSMIC found no significant difference in survival according to treatment pathway, with the exception of the No Surgery group who had a poorer survival consistent with more advanced disease and comorbidity. In line with previous findings, the lack of survival difference for the sequence of surgery suggests equipoise.
INTRODUCTION		
Background / rationale	2	Colorectal cancer is the fourth most common cancer in the UK and contributes to over 700,000 deaths worldwide per year. When first diagnosed, colorectal cancer has already metastasized in 20% of patients to the liver and beyond (termed 'synchronous'). In these patients, 5-year survival is less than 7%. For patients with metastases limited to the liver, surgery and systemic chemotherapy can improve 5-year survival up to 25-40%. Conventional surgery removes the colorectal primary first, followed by chemotherapy, and then resection of the liver metastases. Advances in critical care and innovations such as colonic stenting have allowed liver-first and simultaneous bowel and liver surgery to become viable options. Currently, there is no conclusive evidence to show which approach is optimum, and therefore no standardised clinical pathway.
Objectives	3	To develop the current evidence base and understanding, the CoSMIC inception cohort study has been designed to provide (for the first time) comparable outcome data on patients with colorectal cancer with liver-limited metastatic disease treated by synchronous or sequential surgery. Working to a prospective analysis plan, an exploratory analysis of the data will be performed by applying a hypothesis generating rather than hypothesis testing framework.
Study design	4	Inception cohort study
Setting	5	The study was set in the regional specialist hepato-pancreato-biliary (HPB) cancer service of the Manchester Royal Infirmary in the North West of England, UK, with a referral population of approximately three million people.

	Item	Recommendation
Participants	6	Patients with colorectal cancer and synchronous liver-limited metastatic disease, with the term 'synchronous' defined as patients diagnosed with liver metastases either at the point of presentation or within three months of the primary diagnosis. Inclusion criteria: 1. At least 18 years of age 2. Able to give informed consent 3. Have a histological diagnosis of colorectal cancer 4. No prior history of malignancy 5. Have radiological evidence either on contrast-enhanced CT or MR scanning of hepatic metastatic disease at the time of diagnosis of the primary tumour or within 3 months thereof. Liver biopsies should not be taken to confirm the diagnosis due to the risk of tumour seeding 6. CT and/or [^{18}F]Fluorodeoxyglucose positron emission tomography / computed tomography ([^{18}F]FDG PET/CT) evidence of the absence of extrahepatic metastatic disease or only small, indeterminate pulmonary nodules. 7. MR scan assessment of local stage in those patients with rectal primary tumours 8. WHO performance status 0, 1 and 2 and considered by the MDT to be suitable for surgery and systemic chemotherapy
Variables	7	Baseline staging investigations, predictors of treatment allocation, timelines for completion of the treatment protocol, failure to complete treatment protocol, study outcomes (disease-free survival, disease progression, resection margin status, morbidity profiles, mortality, quality of life)

	Item	Recommendation
Data sources / measurement	8	Case note review and questionnaires for quality of life. Comparisons made between bowel-first, liver-first and synchronous resection groups. Data was collected prospectively using study clinical case report forms. These were anonymised for electronic storage and analysed prospectively during the study to maximise data completion and resolve emergent problems in a timely fashion. The principal source of data was the individual patient records. Vital status beyond the duration of the study was determined through the Demographics Batch Service of the NHS. Data were reported at the end of year 3 allowing for a minimum 12 months outcome data in the entire cohort. It was also proposed (contingent on separate funding) that information on outcome will be collected for up to 10 years from study commencement, providing an informative survival analysis of treatment options.
Bias	9	Selection, detection, attrition bias and confounding.
Study size	10	Based on clinical registers, the HPB unit at the MRI sees approximately 75 patients with colorectal cancer with synchronous liver-limited hepatic metastases per annum. As there are no study-related interventions, recruitment rates were predicted to be high and drop-out low and is estimated to provide 150 patients in the two-year recruitment period. A formal power calculation was not performed for this inception cohort study. Instead, the sample size was informed by the need to provide stable estimates of variance for a range of outcomes; explore the relationship between the treatment pathway and health outcomes; estimate acceptability and recruitment rates; and describe patient and clinician experiences.
Quantitative variables	11	The care of patients within the study pathway was characterised by their principal treatment route as synchronous, liver-first or bowel-first. All patients with data provided outcomes included within analyses, grouped according to the treatment sequence received. Complication profiles in patients according to treatment group were reported. Summary characteristics of patients, patient care provided, and patient outcomes were reported.

	Item	Recommendation
Statistical methods	12	Analyses were conducted to a prospectively agreed analysis plan. Given the exploratory nature of the analysis and multiplicity of comparisons, a hypothesis generating (rather than testing) framework was applied, where statistical significance (arbitrarily at 5%) was viewed as a marker of potential interest for further enquiry. Exploratory analysis of process and clinical outcomes was undertaken to explore the influence of patient, clinician, centre and treatment covariates, using appropriate regression methods. The primary aim is to contrast survival of patients according sequence of care received (Kaplan Meier, log rank test) adjusting for prognostic co-variants (Cox regression). Model building followed a prospectively agreed forward stepwise process.
Participants	13	125 patients in total; 75 patients (60.0%) underwent a bowel-first treatment strategy, 18 patients (14.4%) underwent a liver-first approach, 16 patients (12.8%) underwent a synchronous colorectal and liver resection and 16 patients (12.8%) had no surgery.
Descriptive data	14	Table 1: Patient demographics and details of disease distribution Table 2:Operative details of bowel and liver surgery. Table 3: Chemo(radio)therapy details.
Outcome data	15	Table 4: Peri-operative outcomes. Table 5:Pathway completion.
Main results	16	Table 2: Operative details of bowel and liver surgery. Table 3: Chemo (radio)therapy details. Table 4: Peri-operative outcomes. Table 5: Pathway completion.
Other analyses	17	Appendix 2:Online supplemental data. Cox Regression model. Appendix 3: Quality of life scores (EQ-5D-5L) and EORTC C30. Appendix 4: Quality of life scores (colorectal liver metastasis specific – LM21).
Key results	18	Table 5: Pathway completion Figure 2a: Survival curve by sequence of surgery Figure 2b: Survival curve: staged versus synchronous surgery

	Item	Recommendation
Limitations	19	By design, epidemiological deigns are vulnerable to a number of biases. First, CoSMIC is a relatively small study population. Second, sources of bias include referral bias, ascertainment bias and confounding bias. These biases are acknowledged but it is emphasised that this study is not a report on the management of all patients with stage IV colorectal cancer but rather the subset with potentially resectable liver metastases. Completeness of data was inconsistent for some variables limiting their exploration. With further opportunity the impact of missing data on survival might have been explored with imputation methods as complete data analysis makes strong assumptions. However, data were complete for the principle model generated from the inception cohort.
Interpretation	20	CoSMIC confirms that those who do not or cannot undergo surgery, typically because of a combination of age, co-morbidity and tumor size have less favourable outcome. In terms of pathway, patients with obstructing or perforated cancers were preferentially treated by the bowel-first pathway. The liver-first pathway was selected for patients with left-sided and rectal tumours, in particular those undergoing chemoradiotherapy, but has the highest failure to complete rate. Oncologic and health-care occupancy terms equipoise exist over all three routes in terms of cancer survival, suggesting that there is neither a requirement for nor realistic prospect of clinician/patient support for randomized comparisons of staged versus synchronous surgery for patients with colorectal cancer and synchronous liver metastases as both options confer similar survival. Given the equivalent oncologic outcomes the role and indications of the liver-first route require reconsideration. The data show that chemotherapy can be integrated into treatment pathways. The practical delay between presentation and surgery for patients receiving neoadjuvant chemotherapy was in the order of 6 months. If chemotherapy is used between stages, these data show the importance for formal re-staging prior to proceeding to surgery.
Generalisability	21	Concordance with published literature
Funding	22	This review was supported by a small grant from the Dickinson Trust.

Appendix 2: Online supplemental data table: Cox regression model for the CoSMIC cohort.

Covariate	HR	SE	z	P>|z|	CI		LL	LLR	df	p
Age	1.031	0.015	2.10	0.036	1.002	1.061	-179.201	31.240	3	<0.001
Gender	1.457	0.471	1.16	0.244	0.773	2.746				
Surgery Sequence										
Bowel-first										
Liver-first	0.868	0.439	-0.28	0.780	0.322	2.338				
Synchronous	1.395	0.664	0.70	0.485	0.549	3.547				
No Surgery	9.401	3.465	6.08	0.000	4.565	19.359				

Appendix 3 – Quality of life scores (EQ-5D-5L and EORTC C30 Core Questionnaire)

	All		Bowel-First		Liver-First		Staged Resection		Synchronous Resection		No Surgery
	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	
n	61	36	36	27	8	2	44	29	11	7	6
EQ-5D-5L											
Descriptive score	0.8 (±0.3)	0.8 (±0.2)	0.8 (±0.3)	0.8 (±0.2)	0.7 (±0.3)	0.5 (±0.6)	0.8 (±0.3)	0.8 (±0.2)	0.8 (±0.3)	0.7 (±0.2)	0.6 (±0.1)
Visual analogue scale	74.2 (±21.7)	77.7 (±12.9)	74.2 (±20.3)	78.8 (±13.1)	80.4 (±9.5)	75.0 (±21.2)	75.3 (±18.8)	78.5 (±13.2)	73.4 (±14.8)	74.3 (±11.7)	55.0 (±24.3)
EORTC QLQ-C30 version 3.0											
Global Health Status / QoL	71.7 (±23.9)	74.1 (±18.6)	71.3 (±24.2)	77.5 (±18.0)	77.1 (±11.6)	66.7 (±35.4)	72.3 (±22.4)	76.7 (±18.8)	68.9 (±30.3)	63.1 (±13.5)	47.2 (±19.5)
Functional Scales											
Physical functioning	84.5 (±17.6)	83.1 (±17.0)	84.3 (±19.2)	85.7 (±14.3)	85.8 (±11.5)	53.3 (±37.7)	84.5 (±17.9)	83.4 (±17.6)	84.2 (±16.9)	81.9 (±15.3)	46.7 (±21.9)
Role functioning	75.8 (±28.3)	76.4 (±29.4)	74.1 (±28.9)	79.0 (±29.1)	83.3 (±17.8)	58.3 (±58.9)	75.8 (±27.2)	77.6 (±30.6)	75.8 (±33.6)	71.4 (±24.9)	47.2 (±16.4)
Emotional functioning	82.7 (±20.0)	83.3 (±22.0)	81.9 (±18.8)	87.0 (±18.4)	85.4 (±7.4)	50.0 (±35.4)	82.6 (±17.3)	84.5 (±21.2)	83.3 (±29.3)	78.6 (±26.3)	68.1 (±39.9)
Cognitive functioning	88.2 (±18.6)	87.0 (±20.4)	88.4 (±15.8)	92.0 (±9.7)	89.6 (±12.4)	50.0 (±47.1)	88.6 (±15.2)	89.1 (±16.8)	86.4 (±29.6)	78.6 (±31.5)	75.0 (±23.0)
Social functioning	77.6 (±25.3)	74.5 (±25.0)	75.0 (±25.4)	76.5 (±25.8)	85.4 (±16.5)	50.0 (±23.6)	76.9 (±24.2)	74.7 (±26.2)	80.3 (±30.6)	73.8 (±21.2)	47.2 (±22.2)
Symptom scales / items											
Fatigue	28.7 (±24.7)	29.6 (±23.8)	29.9 (±25.2)	24.3 (±21.1)	27.8 (±8.4)	61.1 (±39.3)	29.5 (±23.0)	26.8 (±23.7)	25.3 (±31.9)	41.3 (±22.0)	57.4 (±27.6)
Nausea and vomiting	6.1 (±13.7)	5.6 (±11.3)	6.9 (±14.6)	3.7 (±7.1)	4.2 (±7.7)	16.7 (±23.6)	6.4 (±13.6)	4.6 (±8.8)	4.5 (±15.1)	9.5 (±18.9)	8.3 (±13.9)
Pain	17.3 (±25.5)	15.7 (±21.4)	15.7 (±21.4)	11.7 (±20.1)	10.4 (±15.3)	33.3 (±47.1)	14.8 (±20.4)	13.2 (±22.0)	27.3 (±39.6)	26.2 (±16.3)	13.9 (±12.5)
Dyspnoea	12.1 (±21.6)	16.7 (±24.6)	9.3 (±17.1)	11.1 (±20.7)	12.5 (±17.3)	33.3 (±47.1)	9.8 (±17.0)	12.6 (±22.6)	21.2 (±34.2)	33.3 (±27.2)	22.2 (±27.2)
Insomnia	23.6 (±29.9)	26.9 (±28.5)	21.3 (±26.6)	21.0 (±24.7)	29.2 (±27.8)	66.7 (±47.1)	22.7 (±26.7)	24.1 (±28.0)	27.3 (±41.7)	38.1 (±30.0)	27.8 (±32.8)
Appetite loss	18.2 (±28.6)	11.1 (±25.2)	18.5 (±29.2)	7.4 (±19.2)	12.5 (±17.3)	16.7 (±23.6)	17.4 (±27.4)	8.0 (±19.2)	21.2 (±34.2)	23.8 (±41.8)	22.2 (±34.4)
Constipation	18.8 (±29.9)	9.3 (±22.0)	13.0 (±26.8)	3.7 (±10.7)	12.5 (±17.3)	0.0 (±0.0)	12.9 (±25.1)	3.4 (±10.3)	42.4 (±36.8)	33.3 (±38.5)	0.0 (±0.0)
Diarrhoea	10.9 (±22.3)	14.8 (±24.5)	7.4 (±14.1)	9.9 (±18.1)	20.8 (±35.4)	50.0 (±70.7)	9.8 (±19.8)	12.6 (±24.3)	15.2 (±31.1)	23.8 (±25.2)	27.8 (±44.3)
Financial difficulties	16.4 (±24.7)	14.8 (±23.2)	18.5 (±27.0)	12.3 (±22.9)	12.5 (±17.3)	50.0 (±23.6)	17.4 (±25.4)	14.9 (±24.5)	12.1 (±22.5)	14.3 (±17.8)	33.3 (±42.2)

Quality of Life measurements. Key: EQ-5D-5L, EuroQol 5 Domain, 5 level QoL questionnaire; EORTC QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Questionnaire version 3.0; QLQ-LMC21, Quality of Life questionnaire Colorectal liver cancer module.

Appendix 4 - Quality of life scores (colorectal liver metastasis specific – LMC21)

	All		Bowel-First		Liver-First		Staged Resection		Synchronous Resection		No Surgery
	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	
n	61	36	36	27	8	2	44	29	11	7	6
EORTC QLQ-C30 version 3.0											
Colorectal liver cancer module: QLQ-LMC21											
Nutritional problems	86.7 (±24.3)	88.4 (±17.3)	86.6 (±23.8)	89.5 (±16.1)	87.5 (±19.4)	75.0 (±35.4)	86.7 (±22.9)	88.5 (±17.3)	86.4 (±30.6)	88.1 (±18.5)	80.6 (±22.2)
Fatigue	66.3 (±28.0)	69.4 (±24.0)	65.7 (±29.0)	73.3 (±23.3)	66.7 (±8.4)	55.6 (±47.1)	65.9 (±26.4)	72.0 (±24.6)	67.7 (±35.3)	58.7 (±18.9)	33.3 (±31.4)
Pain	83.0 (±23.0)	80.9 (±18.9)	84.6 (±20.4)	82.7 (±19.6)	87.5 (±12.5)	77.8 (±15.7)	85.1 (±19.2)	82.4 (±19.1)	74.7 (±34.5)	74.6 (±17.8)	87.0 (±10.9)
Emotional problems	71.1 (±25.0)	69.7 (±27.3)	69.0 (±25.8)	72.5 (±25.2)	74.0 (±9.4)	37.5 (±41.2)	69.9 (±23.7)	70.1 (±27.1)	75.8 (±30.8)	67.9 (±30.2)	59.7 (±20.7)
Weight loss	10.9 (±23.2)	12.0 (±21.3)	12.0 (±25.4)	7.4 (±16.9)	8.3 (±15.4)	33.3 (±47.1)	11.4 (±23.8)	9.2 (±19.7)	9.1 (±21.6)	23.8 (±25.2)	5.6 (±13.6)
Taste	16.4 (±31.3)	12.0 (±22.8)	13.9 (±29.1)	9.9 (±22.3)	25.0 (±38.8)	0.0 (±0.0)	15.9 (±30.9)	9.2 (±21.6)	18.2 (±34.5)	23.8 (±25.2)	22.2 (±17.2)
Dry mouth	21.8 (±28.8)	21.3 (±26.6)	18.5 (±27.0)	22.2 (±27.7)	37.5 (±27.8)	16.7 (±23.6)	22.0 (±27.8)	21.8 (±27.1)	21.2 (±34.2)	19.0 (±26.2)	38.9 (±32.8)
Sore mouth / tongue	12.7 (±26.8)	11.1 (±22.5)	13.0 (±26.8)	9.9 (±22.3)	16.7 (±25.2)	0.0 (±0.0)	13.6 (±26.2)	9.2 (±21.6)	9.1 (±30.2)	19.0 (±26.2)	11.1 (±17.2)
Peripheral neuropathy	22.4 (±34.0)	25.0 (±34.2)	24.1 (±37.0)	25.9 (±33.8)	25.0 (±34.5)	50.0 (±70.7)	24.2 (±36.2)	27.6 (±35.7)	15.2 (±22.9)	14.3 (±26.2)	16.7 (±27.9)
Jaundice	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	0.0 (±0.0)	5.6 (±13.6)
Contact with friends	15.2 (±26.3)	9.3 (±17.1)	15.7 (±25.8)	8.6 (±14.9)	4.2 (±11.8)	33.3 (±47.1)	13.6 (±24.2)	10.3 (±18.0)	21.2 (±34.2)	4.8 (±12.6)	22.2 (±27.2)
Talking about feelings	6.7 (±21.7)	14.8 (±21.7)	7.4 (±21.2)	11.1 (±18.5)	0.0 (±0.0)	50.0 (±23.6)	6.1 (±19.4)	13.8 (±20.9)	9.1 (±30.2)	19.0 (±26.2)	22.2 (±34.4)
Sex	31.5 (±36.5)	28.7 (±36.6)	31.5 (±35.6)	27.2 (±35.8)	41.7 (±34.5)	50.0 (±70.7)	33.3 (±35.2)	28.7 (±37.5)	24.2 (±42.4)	28.6 (±35.6)	61.1 (±44.3)

Quality of Life measurements. Key: EQ-5D-5L, EuroQol 5 Domain, 5 level QoL questionnaire; EORTC QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Questionnaire version 3.0; QLQ-LMC21, Quality of Life questionnaire Colorectal liver cancer module.