Quality of life from a randomized controlled trial of laparoscopic or open liver resection for colorectal liver metastases

Å. A. Fretland[1,2,8], V. J. Dagenborg[3,4,8], G. M. Waaler Bjørnelv[1,9], D. L. Aghayan[1,8,14], A. M. Kazaryan[1,11,13,14], L. Barkhatov[1,8,12], R. Kristiansen[1,5], M. W. Fagerland[7], B. Edwin[1,2,8] and M. H. Andersen[6,10]

[1]The Intervention Centre, Departments of [2]Hepato-Pancreato-Biliary Surgery, [3]Tumour Biology, [4]Gastroenterological Surgery, [5]Information Technology and [6]Transplantation Medicine, and [7]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Departments of [8]Clinical Medicine, [9]Health Management and Health Economics and [10]Health Science, University of Oslo, Oslo, [11]Department of Gastrointestinal Surgery, Vestfold Hospital Trust, Tønsberg, and [12]Department of Gastrointestinal Surgery, Haukeland University Hospital, Bergen, Norway, [13]Department of Faculty Surgery 2, I. M. Sechenov First Moscow State Medical University, Moscow, Russia, and [14]Department of Surgery 1, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

Correspondence to: Dr Å. A. Fretland, The Intervention Centre, Oslo University Hospital, Pb. 4950 Nydalen, 0424 Oslo, Norway (e-mail: aasmund@fretland.no)

Presented to the International Association for Hepato-Pancreato-Biliary Association Congress, Geneva, Switzerland, September 2018

(*Health related quality of life after laparoscopic and open liver resection. data from the OSLO-COMET randomized controlled trial. Fretland, Å.A. et al.,HPB, Volume 20, S215.* https://doi.org/10.1016/j.hpb.2018.06.098*)*

Background: Most treatments for cancer cause a decline in patients' health-related quality of life (HRQoL). Limiting this decline is a universal goal for healthcare providers. Using minimally invasive instead of open surgical techniques might be one way to achieve this. The aim of this study was to compare postoperative HRQoL after open and laparoscopic liver resection.

Methods: This was a predefined substudy of an RCT comparing open with laparoscopic liver resection. Patients with colorectal liver metastases were assigned randomly to open or laparoscopic parenchyma-sparing liver resection. HRQoL was assessed with the Short Form 36 questionnaire at baseline, and 1 and 4 months after surgery.

Results: A total of 280 patients were randomized, of whom 273 underwent surgery (129 laparoscopic, 144 open); 682 questionnaires (83.3 per cent) were available for analysis. One month after surgery, patients in the laparoscopic surgery group reported reduced scores in two HRQoL domains (physical functioning and role physical), whereas those in the open surgery group reported reduced scores in five domains (physical functioning, role physical, bodily pain, vitality and social functioning). Four months after surgery, HRQoL scores in the laparoscopic group had returned to preoperative levels, whereas patients in the open group reported reduced scores for two domains (role physical and general health). The between-group difference was statistically significant in favour of laparoscopy for four domains after 1 month (role physical, bodily pain, vitality and social functioning) and for one domain after 4 months (role physical).

Conclusion: Patients assigned to laparoscopic liver surgery reported better postoperative HRQoL than those assigned to open liver surgery. For role limitations caused by physical health problems, patients in the laparoscopic group reported better scores up to 4 months after surgery. Registration number: NCT01516710 (http://www.clinicaltrials.gov).

+A: Introduction

Colorectal cancer is the third most common cancer worldwide, with nearly 1.4 million new cases diagnosed annually, and almost 700 000 deaths[1]. Half of patients develop distant metastases, and many of these require repeated surgical and oncological treatment. The prognosis for colorectal cancer has improved with new treatments[2,3], but many of these have severe side-effects[4]. Therefore, an increasing number of cancer survivors live with side-effects of the treatment that initially saved their lives. Treatments may have similar survival outcomes but different side-effects. Thus, patient-reported outcomes, such as health-related quality of life (HRQoL), are important to assess the impact of treatment on the patient's daily life. Furthermore, HRQoL data can be converted to quality-adjusted life-years (QALYs), which are used in cost–utility analysis of different treatments[5,6] .As healthcare resources are limited, decision-makers increasingly demand such analyses when prioritizing between treatments.

Surgical resection is currently the only potentially curative treatment for colorectal cancer liver metastases[7]. HRQoL deteriorates after liver resection, usually temporarily, but occasionally permanently. In a prospective study[8] of patients undergoing open liver resection, HRQoL was reduced up to 3 months after operation, but had returned to baseline after 6 months. Data on HRQoL after laparoscopic liver resection are limited[9–11]. Several randomized studies have compared laparoscopic with open resection of primary colorectal tumours, including effects on HRQoL. Although some studies[12] reported improved short-term HRQoL after laparoscopic treatment, others[13,14] found only little or no difference. In a randomized study[15] comparing laparoscopic with open living donor nephrectomy, laparoscopy was only significantly better for the domain bodily pain 1 month after surgery.

The OSLO-COMET (Oslo Randomized Laparoscopic *Versus* Open Liver Resection for Colorectal Metastases) randomized trial[16] was undertaken to compare laparoscopic and open parenchyma-sparing liver resection of colorectal cancer liver metastases (CLM). Parenchyma-

sparing resection was defined as resection of less than three consecutive segments. Multiple resections in one patient were allowed. The aim of this substudy of OSLO-COMET was to compare HRQoL up to 4 months after operation in patients assigned randomly to either open or laparoscopic liver resection for CLM.

+A: Methods

This was a preplanned substudy of the OSLO-COMET trial. The protocol and short-term results have been published previously[16,17]. Patients were assigned randomly to undergo open or laparoscopic parenchyma-sparing liver resection after giving written informed consent.

All patients were asked to fill out paper versions of the 36-item Medical Outcomes Study Short Form 36 (SF-36®, Norwegian version 2.0; Quality Metric Inc., Lincoln, RI, US) in the outpatient clinic before surgery, then at follow-up visits 1 and 4 months after operation. Paper questionnaires were returned by mail, and entered manually into the SF-36® scoring software by two researchers, who were blinded to the trial intervention.

Patients in the trial were treated according to the Norwegian guidelines for treatment of metastatic colorectal cancer[18]. In general, patients with synchronous CLM**,** performance status 0–1 and a raised CEA level received chemotherapy after removal of the primary tumour. The treatment usually comprised four courses of oxaliplatin-based chemotherapy, followed by liver surgery and an additional eight courses. Patients with metachronous liver metastases received 12 courses of adjuvant chemotherapy after resection of the primary tumour if cancer cells were found in regional lymph nodes. These patients, who would often have received 12 courses of oxaliplatin-based chemotherapy, rarely received adjuvant chemotherapy after liver surgery. Patients with primary tumours in the rectum did not receive adjuvant chemotherapy after surgery for the primary cancer. These patients received adjuvant chemotherapy following liver surgery after an individual assessment.

+B: Measures

The SF-36® was used to assess HRQoL[19]. The SF-36® includes one multi-item scale measuring the following health domains. Physical functioning refers to the extent to which the respondent's perception of quality of life is limited or influenced by their physical condition. Role limitation refers to the extent to which the respondent's performance of roles in daily activities is impeded by the physical state of health. Bodily pain indicates to what extent the respondent's experience of bodily pain hinders performance of daily activities, including work-related duties in the public domain and tasks within the home environment. General health is measured in terms of excellent, very good, good, fair or poor, getting ill more easily than other people, and just as healthy as anyone they know. Vitality refers to feeling energetic or fatigued. Social functioning refers to social activities and interaction with significant others such as family members, friends, neighbours and other social relationships. Role emotional assesses the extent to which the emotional condition of the respondent limits daily functioning. Mental health is measured in terms of how the respondent is feeling with respect to anxiety, depression, loss of emotional control and psychological well-being. Scores for each dimension ranged from 0 to 100, with a higher score indicating better health status. SF-36® has been translated into several languages, and tested for psychometric properties in a number countries including Norway, with internal consistency (Cronbach's α) ranging from 0.80 (role emotional) to 0.93 (bodily pain).

The data set presented in this study was used to calculate QALYs for the cost-effectiveness analysis published previously from the OSLO-CoMeT trial[16].

+B: Statistical analysis

The sample size for this study was based on the power calculation for the primary endpoint of OSLO-CoMeT (280 patients)[16]. However, to ensure that the present study was not underpowered, a second power calculation was undertaken, which estimated 50 patients in each group would be sufficient, based on a two-sided α of 0.05 and 80 per cent power[15]. An

improvement of 6–15 points or a deterioration of 9–17 points on a scale from 0 to 100 was considered clinically significant[20], and the effect expectancy for between-group differences was set at 0.6. A drop-out rate of 30 per cent was estimated, and so the sample size necessary to detect a 0.6 effect expectancy was 60 patients (with at least 2 completed HRQoL forms) in each group. The statistical analyses were based on a modified intention-to-treat analysis. Thus, patients whose procedure was converted from laparoscopic to open liver resection were analysed in the laparoscopic group. However, patients who were randomized but did not undergo surgery were excluded.

A linear mixed model was fitted to each domain of SF-36®. Each model contained a fixed effect for treatment (laparoscopic *versus* open surgery), adjuvant therapy (yes/no), time (measured in weeks after surgery), treatment × time interaction and a random intercept. The time development was modelled as piecewise linear, with a knot at 1 month after surgery, so the models allowed for one development from surgery to 1 month after surgery, and another development from 1 to 4 months after surgery. Based on linear mixed models, mean treatment group values (with 95 per cent confidence intervals) were estimated for three time points: baseline (time of operation), and 1 and 4 months after surgery. Mean changes in each group were estimated from baseline to 1 month after surgery, and from baseline to 4 months after surgery. Between-group differences in change from baseline to 1 and 4 months after surgery were also calculated. Adjuvant chemotherapy might have influenced HRQoL at 4 months (no patient commenced chemotherapy before 1 month after operation). For this reason, adjuvant chemotherapy was added as a factor in the statistical model used to calculate between-group differences. A similar analysis was undertaken to estimate the role of postoperative morbidity on HRQoL. In this analysis, postoperative morbidity, represented by the Comprehensive Complication Index[21] score for each patient, was added as a factor in the analysis of between-

group differences. Statistical analyses were performed with Stata® version 14 (StataCorp, College Station, Texas, USA).

The 30-day complication rate was compared between the 2 treatment groups using Fisher Mid-P test for association. The difference between the treatment group probabilities of having a complication within 30 days (the risk difference) was estimated with a 95% Newcombe hybrid score CI. Intraoperative and postoperative outcomes were analyzed with a median regression, which provided a 95% CI for the difference between the medians of the 2 treatment groups and a P value for the null hypothesis of equal medians. A 2-sample t test was used when the median was not a relevant measure to compare the treatment groups.

The pattern of missing data was analysed by means of logistic regression, using age, sex, baseline HRQoL, baseline co-morbidity and time of inclusion in the trial as co-variables. Details of this analysis can be found in the supplementary appendix of the paper reporting the primary endpoint of OSLO-COMET.

+A: Results

A total of 280 patients were included in OSLO-COMET, and 273 underwent surgery. Of these, 244 patients completed at least two questionnaires, but all questionnaires were included in the modified intention-to-treat analysis. Patient characteristics were similar in both groups (*Tables 1* and *2*). In total, 682 questionnaires (83.3 per cent) were available for analysis; 255 (93.4 per cent) at baseline, 224 (82.1 per cent) at 1 month and 203 (74.4 per cent) at 4 months. Questionnaires were found to be missing at random, except that late inclusion in the trial was associated with an increased chance of questionnaires being missing compared with early inclusion. There was no association between type of surgery and missing questionnaires.

+B: Patient-reported outcomes

Mean scores and within-group changes in scores for the SF-36® domains are shown in *Table 3*. At baseline, scores were similar in the two groups. At 1 month, patients in the laparoscopic

group reported reduced scores for the physical functioning and role physical domains compared with baseline, whereas those in the open group reported reduced scores for physical functioning, role physical, bodily pain, vitality and social functioning. At 4 months, scores in the laparoscopic group had returned to preoperative levels, but patients in the open group reported reduced scores for role physical and general health. Patients in both groups reported increased scores for mental health at 1 month after surgery.

Between-group differences in changes are shown in *Table 4*. The open group reported a significantly larger change than the laparoscopic group for role physical, bodily pain, vitality and social functioning at 1 month, and for role physical at four months.

In total, 53 patients (41.1 per cent) in the laparoscopic group and 76 (52.8 per cent) in the open group received adjuvant chemotherapy. Seven patients in the laparoscopic and eight in the open group had liver resection before surgery for the primary tumour. These patients underwent liver resection shortly after completion of neoadjuvant radiochemotherapy for rectal cancer, and then rectal resection 6–10 weeks later. A subgroup analysis without these patients did not alter the findings of the study. Similarly, adjustments for adjuvant chemotherapy or postoperative morbidity did not change the results.

+A: Discussion

In this RCT, patients assigned to laparoscopic liver surgery reported better postoperative HRQoL than those assigned to open liver surgery. For the role physical domain, the difference was seen up to 4 months after operation. SF-36® has previously been validated as a measure of postoperative recovery after colorectal surgery[22]. The present findings suggest that SF-36® is also valid for liver surgery, and for measuring differences between open and laparoscopic liver surgery. Furthermore, the findings suggest important patient benefits for those having laparoscopic surgery compared with patients undergoing open surgery. Reduced scores in the domain role physical indicate problems with performing of roles in daily life,

and a need to reduce the amount of time spent on work or other activities. Reduced scores in the domain general health indicate a perception of poorer personal health. The results confirm, with a high level of evidence, the common belief that postoperative recovery is faster after laparoscopic compared with open liver surgery.

In 2012, Rees and colleagues[8] reported that patients' functional aspects of health decreased up to 3 months after open liver surgery, but recovered by 6 months. In the present study, patients in the open group reported reduced functional aspects of health by 4 months, but were expected to regain preoperative function by 6–12 months after the procedure. Thus, the findings are in line with the existing literature on open liver surgery. To examine long-term HRQoL, all surviving patients in the present study will be asked to complete a new SF-36® form 2 years after surgery.

At 1 month, there was a difference of between 6 and 13 points in favour of laparoscopy for four domains. A difference of this magnitude is expected to be of real clinical significance[20], as returning to regular daily activities and normal life as soon as possible after treatment is expected to be of great importance for patients with metastatic colorectal cancer.

Interestingly, in a study of patients undergoing open or laparoscopic pancreatoduodenectomy for adenocarcinoma, Croome and colleagues[23] reported that a higher proportion of patients in the open group compared with the laparoscopic group had a delay in starting adjuvant chemotherapy, or did not receive it at all. Similar results were found in two studies that used propensity score analysis to compare laparoscopic and open liver surgery[24,25]. Postoperative complications have also been found to be associated with omission of adjuvant chemotherapy after colorectal cancer surgery[26].

In the present study, there was no difference in time to initiation of chemotherapy. A referral to the medical oncologist was made only after the formal histology report had been received 4 weeks after operation. The referral process usually took 2 weeks to complete.

Thus, a possible benefit would be hidden by this 6-week wait. Furthermore, patients in both groups received a median of eight courses of adjuvant chemotherapy, suggesting that open surgery was also well tolerated. This is in line with a hospital stay of just over 4 days in the open group[16]. However, in a study of perioperative FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) chemotherapy in patients having surgery for CLM, only patients with good performance status had benefit from the treatment in terms of improved progression-free survival[27]. Applied to the present patients, it could be speculated that patients in the laparoscopic group who started adjuvant chemotherapy with better HRQoL might have benefitted more from chemotherapy or tolerated more aggressive treatment, such as more courses of oxaliplatin. It was not possible to obtain a detailed overview of the type of adjuvant treatment patients received in this study.

The primary outcome of this trial was a reduced postoperative morbidity rate in the laparoscopic group. An interesting question is whether reduced morbidity was the sole cause of improved HRQoL in the present study. However, analysis of between-group differences in HRQoL with adjustment for postoperative morbidity did not change the results. It would therefore seem to be the effect of laparoscopy itself, and not the reduction in morbidity, that yielded the HRQoL benefit.

A main limitation of this study is the lack of blinding. However, most patients would recognize the type of surgery by seeing the operation wound, which in a blinded surgery trial usually happens during the first week after operation. In the ongoing double-blind Orange II plus trial of open *versus* laparoscopic hemihepatectomy (NCT01441856), the operative procedure is revealed to the patient only after 5 days. Thus, not even a double-blind trial design would prevent the patient's expectations from interfering with long-term HRQoL results. Furthermore, it is challenging to achieve proper double-blinding in a surgical RCT and, unless performed and reported according to strict guidelines, it may be of little value[28].

It is important to stress that OSLO-COMET was a single-centre trial, carried out at a high-volume institution for both liver surgery and laparoscopic hepatobiliary surgery. The present results are probably generalizable to similar high-volume institutions.

An analysis of cancer-specific outcomes after open and laparoscopic liver resection is needed. At present, the follow-up of trial participants is not complete, so oncological outcomes cannot be reported here.

All patients in this study had parenchyma-sparing liver resections. An increasing number of patients with CLM are being treated with parenchyma-sparing techniques, facilitating repeat resection in the event of disease recurrence[29-31] At Oslo University Hospital, patients have undergone as many as four subsequent liver resections for recurrent metastases. When several operations are necessary, the impairment of HRQoL after each operation might be even more important, and laparoscopic surgery in these patients may also have an additive effect on the patient's HRQoL.

Laparoscopic liver surgery is relevant for conditions other than cancer. In living donor transplantation, postoperative HRQoL is of importance, not only socioeconomically but also for the donation rate. Laparoscopic living donor nephrectomy was reported to double the living donor transplantation rate after its introduction in the mid-1990s and is now the standard of care in most transplant centres[32]. Laparoscopic living donor hepatectomy is still controversial, especially in Western countries, mostly because of the fear of donor morbidity[33]. However, access to donor organs is limited and living donor programmes have successfully increased the hepatic donor pool. Laparoscopic left lateral sectionectomy has been proposed as standard practice for paediatric recipients, but lack of evidence and technical challenges have halted its development[34]. The results from the present study may also applicable be to the donor population, and the findings may further ease the implementation of laparoscopic living donor hepatectomy.

For patients who survive metastatic colorectal cancer, quality of life during and after treatment is certainly important. However, patients who develop early recurrence might be the ones who benefit most from minimally invasive techniques. The months between surgery and first follow-up imaging might be the only cancer-free time these patients have left. Living with minimal limitations related to surgical treatment might be even more important to patients with a short life expectancy than to long-term survivors.

+A: Acknowledgements

The study was funded by South-East Norway Health Authority (grant 201135 to Å.A.F., grant 201622 to G.M.W.B.) and the Research Council of Norway (grant 218325 to V.J.D.).

Disclosure: The authors declare no conflict of interest.

+A: References

1 Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87–108.

2 Quaresma M, Coleman MP, Rachet B. 40-year trends in an index of survival for all cancers combined and survival adjusted for age and sex for each cancer in England and Wales, 1971–2011: a population-based study. *Lancet* 2015; **385**: 1206–1218.

3 <B>Larsen IK (ed.). *Cancer in Norway 2013*. Cancer Registry of Norway: Oslo, 2015.

4 Braun MS, Seymour MT. Balancing the efficacy and toxicity of chemotherapy in colorectal cancer. *Ther Adv Med Oncol* 2011; **3**: 43–52.

5 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002; **21**: 271–292.

6 <B>Drummond MF, Drummond F. *Methods for the Economic Evaluation of Health Care Programmes* (3rd edn). Oxford University Press: Oxford, 2005.

7 Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M *et al.* Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; **25**: 4575–4580.

8 Rees JR, Blazeby JM, Fayers P, Friend EA, Welsh FK, John TG *et al.* Patient-reported outcomes after hepatic resection of colorectal cancer metastases. *J Clin Oncol* 2012; **30**: 1364–1370.

9 Makki K, Chorasiya VK, Sood G, Srivastava PK, Dargan P, Vij V. Laparoscopy-assisted hepatectomy *versus* conventional (open) hepatectomy for living donors: when you know better, you do better. *Liver Transpl* 2014; **20**: 1229–1236.

10 Marubashi S, Wada H, Kawamoto K, Kobayashi S, Eguchi H, Doki Y *et al.* Laparoscopy-assisted hybrid left-side donor hepatectomy. *World J Surg* 2013; **37**: 2202–2210.

11 Giuliani A, Migliaccio C, Ceriello A, Aragiusto G, La Manna G, Calise F. Laparoscopic *vs.* open surgery for treating benign liver lesions: assessing quality of life in the first year after surgery. *Updates Surg* 2014; **66**: 127–133.

12 Janson M, Lindholm E, Anderberg B, Haglind E. Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer. *Surg Endosc* 2007; **21**: 747–753.

13 Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G; Clinical Outcomes of Surgical Therapy (COST) Study Group. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy *vs* open colectomy for colon cancer: a randomized trial. *JAMA* 2002; **287**: 321–328.

14 Andersson J, Angenete E, Gellerstedt M, Angerås U, Jess P, Rosenberg J *et al.* Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial. *Br J Surg* 2013; **100**: 941–949.

15 Andersen MH, Mathisen L, Veenstra M, Oyen O, Edwin B, Digernes R *et al.* Quality of life after randomization to laparoscopic *versus* open living donor nephrectomy: long-term follow-up. *Transplantation* 2007; **84**: 64–69.

16 Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW *et al.* Laparoscopic *versus* open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. *Ann Surg* 2018; **267**: 199–207.

17 Fretland ÅA, Kazaryan AM, Bjørnbeth BA, Flatmark K, Andersen MH, Tønnessen TI *et al.* Open versus laparoscopic liver resection for colorectal liver metastases (the Oslo-CoMet study): study protocol for a randomized controlled trial. *Trials* 2015; **16**: 73.

18 <EPATH>Guldvog B. *Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av kreft i tykktarm og endetarm* (5th edn); 2017. http://www.helsedirektoratet.no/publikasjoner/ [accessed ??].

19 <B>Maruish ME. *User's Manual for the SF-36v2 Health Survey* (3rd edn). QualityMetric Inc., Lincoln, RI, US, 2011.

20 Kvam AK, Fayers P, Wisloff F. What changes in health-related quality of life matter to multiple myeloma patients? A prospective study. *Eur J Haematol* 2010; **84**: 345–353.

21 Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013; **258**: 1–7.

22 Antonescu I, Carli F, Mayo NE, Feldman LS. Validation of the SF-36 as a measure of postoperative recovery after colorectal surgery. *Surg Endosc* 2014; **28**: 3168–3178.

23 Croome KP, Farnell MB, Que FG, Reid-Lombardo KM, Truty MJ, Nagorney DM *et al.* Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? *Ann Surg* 2014; **260**: 633–638.

24 Mbah N, Agle SC, Philips P, Egger ME, Scoggins CR, McMasters KM *et al.* Laparoscopic hepatectomy significantly shortens the time to postoperative

chemotherapy in patients undergoing major hepatectomies. *Am J Surg* 2017; **213**: 1060–1064.

25 Kawai T, Goumard C, Jeune F, Savier E, Vaillant JC, Scatton O. Laparoscopic liver resection for colorectal liver metastasis patients allows patients to start adjuvant chemotherapy without delay: a propensity score analysis. *Surg Endosc* 2018; **32**: 3273–3281.

26 Hendren S, Birkmeyer JD, Yin H, Banerjee M, Sonnenday C, Morris AM. Surgical complications are associated with omission of chemotherapy for stage III colorectal cancer. *Dis Colon Rectum* 2010; **53**: 1587–1593.

27 Sorbye H, Mauer M, Gruenberger T, Glimelius B, Poston GJ, Schlag PM *et al.*; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK (CRUK); Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Predictive factors for the benefit of perioperative FOLFOX for resectable liver metastasis in colorectal cancer patients (EORTC Intergroup Trial 40983). *Ann Surg* 2012; **255**: 534–539.

28 Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can J Surg*. 2010 Oct; **53**: 345–348.

29 Gold JS, Are C, Kornprat P, Jarnagin WR, Gonen M, Fong Y, *et al.* Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. *Annals of Surgery*. 2008 Jan; **247**: 109–117.

30 Postriganova N, Kazaryan AM, Kazaryan AM, Røsok BI, Fretland AA, Barkhatov L, *et al.* Margin status after laparoscopic resection of colorectal liver metastases: does a narrow resection margin have an influence on survival and local recurrence? *HPB (Oxford)*. 2014 Sep; **16**: 822–829.

31 Montalti R, Tomassini F, Laurent S, Smeets P, De Man M, Geboes K, *et al.* Impact of surgical margins on overall and recurrence-free survival in parenchymal-

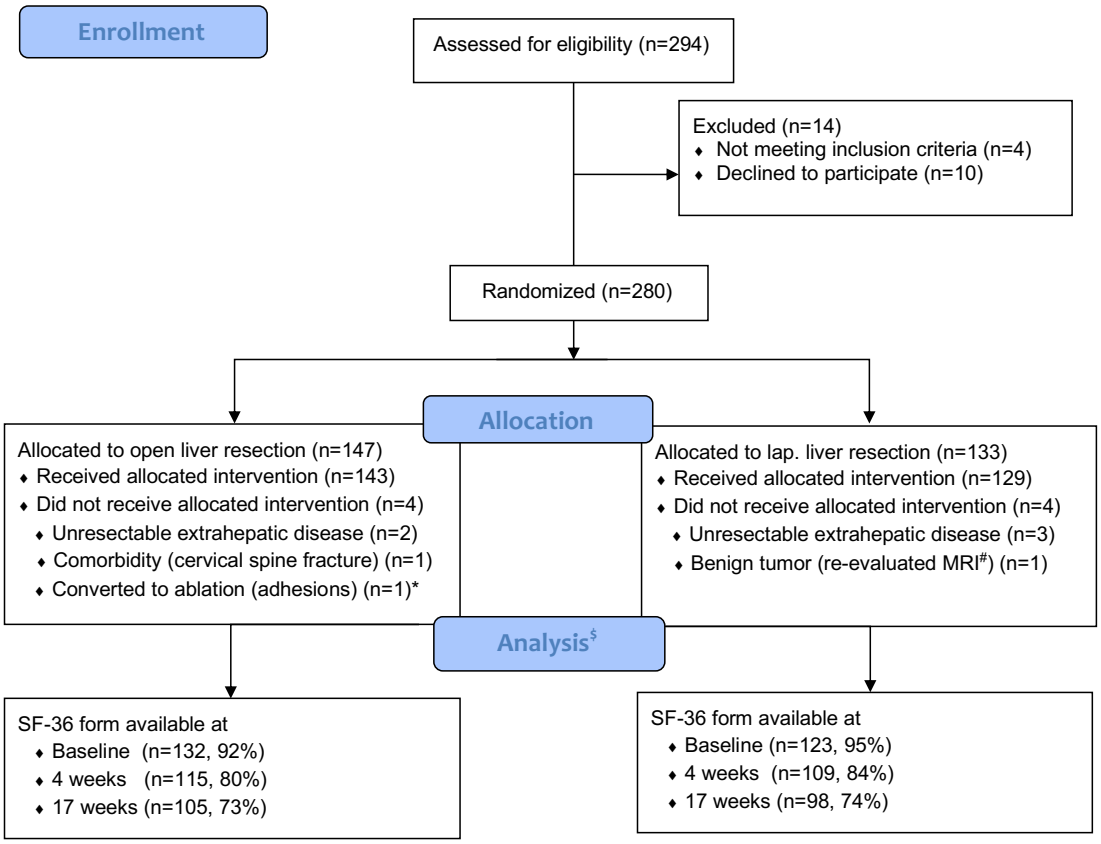
sparing laparoscopic liver resections of colorectal metastases. *Surg Endosc*. Springer US; 2015 Sep; **29**: 2736–2747.

32 Soubrane O, de Rougemont O, Kim K-H, Samstein B, Mamode N, Boillot O, *et al.* Laparoscopic Living Donor Left Lateral Sectionectomy: A New Standard Practice for Donor Hepatectomy. *Annals of Surgery*. 2015 Nov; **262**: 757–61–discussion761–3.

33 Cauchy F, Schwarz L, Scatton O, Soubrane O. Laparoscopic liver resection for living donation: where do we stand? *World J Gastroenterol*. 2014 Nov 14; **20**: 15590–15598.

34 Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS *et al.* Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015; **261**: 619–629.

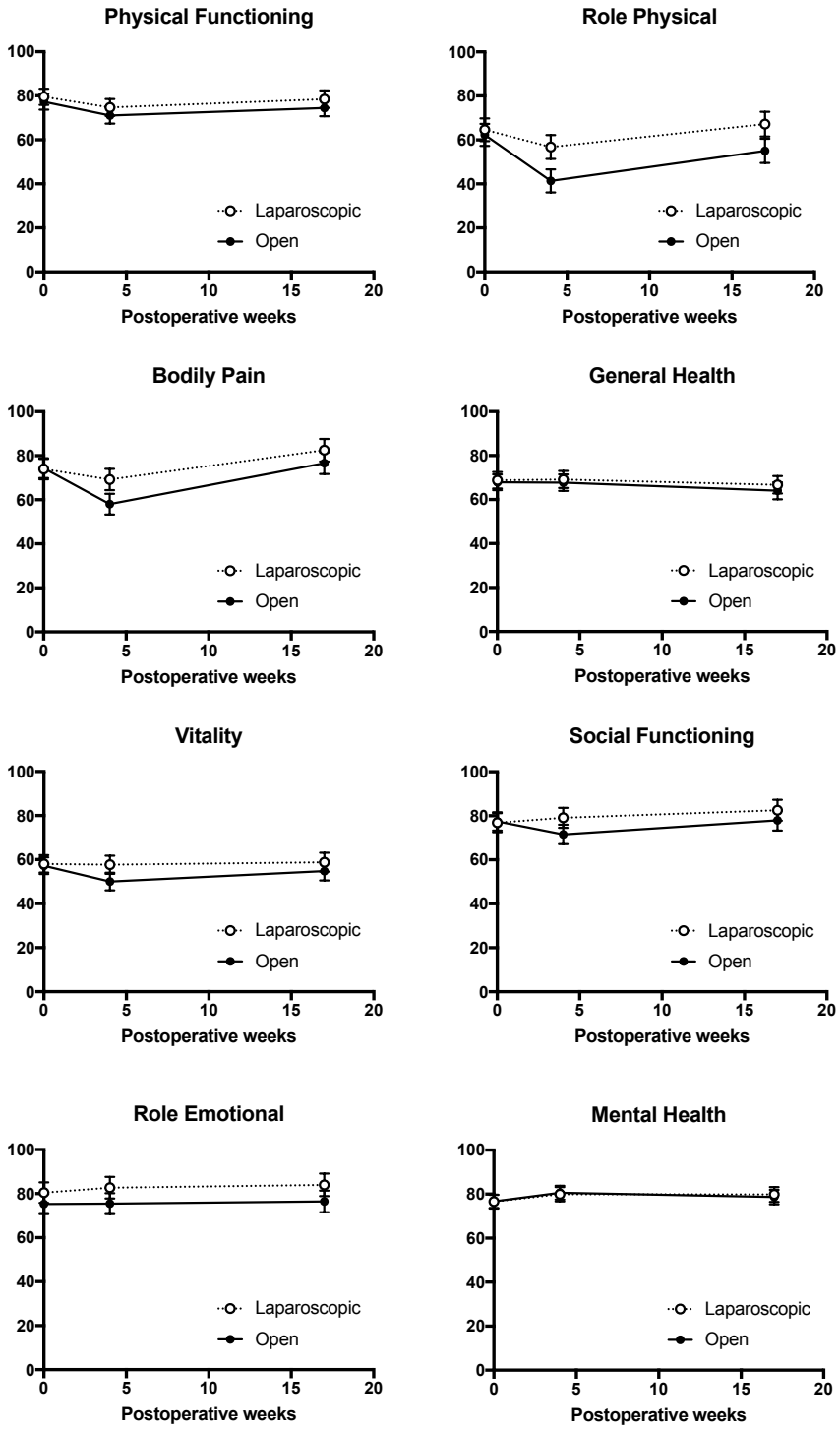
Fig. 1 CONSORT flow chart for the trial



* This patient was included in the Modified Intention-to-Treat analysis
$ Modified Intention-to-Treat
# MRI denotes Magnetic Resonance Imaging

*Patient included in modified intention-to-treat analysis. SF, Short Form.

Fig. 2 Short Form 36 scores after laparoscopic or open surgery



a Physical functioning, **b** role physical, **c** bodily pain, **d** general health, **e** vitality, **f** social functioning, **g** role emotional and **h** mental health. Error bars represent 95 per cent confidence intervals. Values were estimated by a linear mixed model.

Table 1 Baseline characteristics (intention-to-treat population)

	Laparoscopic (*n* = 133)	Open (*n* = 147)
Age (years)*	67(8)	66(10)
Sex ratio (M : F)	77 : 56	87 : 60
BMI (kg/m^2)*	26(5)	25(4)
ECOG score		
0	111 (85.4)	111 (81.6)
1	18 (13.8)	23 (16.9)
2	1 (0.8)	2 (1.5)
Missing	3	11
ASA fitness grade		
I	11 (9.0)	20 (14.6)
II	59 (48.4)	73 (53.3)
III	51(41.8)	44(32.1)
IV	1 (0.8)	0 (0)
Missing	11	10
No. of metastases*	1.5(1.1)	1.6(1.1)
Primary rectal tumour	50 of 128 (39.0)	62 of 142 (43.6)
Synchronous metastases	75 (56.4)	91 (61.9)
Chemotherapy before surgery	77 (57.9)	99 (67.3)
CEA, μg/L†	4 (1–200)	4 (1–128)
Previous liver resection	23 (17.3)	13 (8.8)
Clinical Risk Score†	2 (1–2)	2 (1–2)
Basingstoke Predictive Index score†	5 (3–12)	5 (2–12)
Modified Iwate complexity score†	6 (2–11)	6 (2–11)
Modified liver surgery complexity score	1.99 (1.36 to 6.75)	1.36 (1.36 to 7.36)
Liver-first approach	7 (5.3)	8 (5.4)

Values in parentheses are percentages unless indicated otherwise; values are *mean(s.d.) and †median (i.q.r.). ECOG, Eastern Cooperative Oncology Group. CEA, carcinoembryonic antigen.

Table 2 Perioperative results for the modified intention-to-treat population (only patients who underwent surgery)

	Laparoscopic (*n* = 129)	Open (*n* = 144)	*P*
Postoperative complications ≥ Accordion grade 2	24 (18.6)	44 (30.6)	0.021
Comprehensive Complication Index score*	5.2 (3.1, 7.3)	9.3 (6.6, 12.0)	0.021
Conversion			
To laparotomy	2 (1.6)	–	
To hand-assisted	7 (5.4)	–	
Duration of postoperative hospital stay (h)†	53 (45, 61)	96 (89, 103)	< 0.001
Adjuvant chemotherapy within 4 months	53 (41.1)	76 (52.8)	0.068
Any chemotherapy within 4 months	57 (44.2)	77 (53.5)	0.150
Weight of pathology specimen (g)‡	83 (38–185)	64 (31–204)	
Time to adjuvant chemotherapy (days)†	47 (40, 54)	44 (37, 51)	0.556
No. of adjuvant courses†	8 (6, 10)	8 (6, 10)	1.000

Values in parentheses are percentages unless indicated otherwise; values are *mean (95 per cent c.i.), †median (95 per cent c.i.) and ‡median (i.q.r.). Medians are compared with median regression, means are compared with student's t-test, frequencies are compared with Fishers mid -P test.

Table 3 Short Form 36 domain scores and within-group changes at 1 and 4 months after laparoscopic or open liver resection

	Mean score at baseline	Mean score at 1 month	Mean score at 4 months	Change from baseline to 1 month	*P*	Change from baseline to 4 months	*P*
Physical functioning							
Laparoscopic	80 (76, 83)	75 (71, 79)	78 (75, 82)	–5 (–8, –1)	0.005	–1 (–5, 2)	0.558
Open	77 (73, 81)	71 (67, 75)	74 (71, 82)	–6 (–10, –3)	0.001	–3 (–6, 1)	0.113
Role physical							
Laparoscopic	65 (59, 70)	57 (51, 62)	67 (62, 73)	–8 (–14, –2)	0.007	3 (–3, 8)	0.392
Open	62 (57, 67)	41 (36, 47)	55 (50, 61)	–21 (–27, –15)	< 0.001	–7 (–13, –1)	0.014
Bodily pain							
Laparoscopic	74 (69, 79)	69 (64, 74)	83 (77, 88)	–5 (–10, 1)	0.096	9 (3, 14)	0.004
Open	74 (70, 79)	58 (53, 63)	77 (72, 82)	–16 (–22, –11)	< 0.001	2 (–3, 8)	0.435
General health							
Laparoscopic	69 (65, 73)	69 (65, 73)	67 (62, 72)	0 (–3, 4)	0.840	–2 (–6, 2)	0.277
Open	68 (64, 71)	68 (64, 71)	62 (57, 67)	0 (–4, 3)	0.930	–4 (–7, 0)	0.035
Vitality							
Laparoscopic	58 (54, 62)	58 (54, 62)	59 (55, 63)	0 (–5, 4)	0.850	1 (–4, 5)	0.738
Open	57 (53, 61)	50 (46, 54)	55 (51, 59)	–7 (–11, –3)	0.001	–2 (–7, 2)	0.248
Social functioning							
Laparoscopic	77 (73, 81)	79 (75, 84)	83 (78, 87)	2 (–3, 7)	0.396	6 (0, 11)	0.038
Open	77 (73, 82)	72 (67, 76)	78 (73, 83)	–6 (–11, –1)	0.020	0 (–5, 6)	0.854
Role emotional							
Laparoscopic	80 (76, 85)	83 (78, 88)	84 (79, 89)	2 (–3, 8)	0.405	4 (–2, 9)	0.207
Open	75 (71, 80)	75 (71, 80)	76 (72, 81)	1 (–4, 7)	0.933	1 (–4, 7)	0.655
Mental health							
Laparoscopic	77 (73, 80)	80 (77, 83)	80 (76, 83)	3 (0, 7)	0.042	3 (0, 7)	0.055
Open	77 (74, 80)	81 (78, 84)	79 (75, 82)	4 (1, 7)	0.013	2 (–1, 5)	0.224

Values in parentheses are 95 per cent confidence intervals. The analysis included only patients who completed at least one Short Form 36 questionnaire (laparoscopic, 127; open, 143). Values were estimated by a linear mixed model.

Table 4 Between-group differences in change at 1 and 4 months after laparoscopic and open liver resection

	Between-groups difference in changes from baseline to 1 month	*P*	Between-group difference in changes from baseline to 4 months	*P*
Physical functioning	–1.4 (–6.1, 3.3)	0.564	–1.8 (–6.7, 3.2)	0.484
Role physical	–13.1 (–21.1, –5.1)	0.001	–9.9 (–18, –1.6)	0.019
Bodily pain	–11.6 (–19.4, –3.8)	0.003	–6.3 (–14.4, 1.7)	0.124
General health	0.4 (–3.2, 3.9)	0.837	–1.8 (–7.0, 3.3)	0.490
Vitality	–6.8 (–12, –1.0)	0.023	–3.2 (–9.3, 2.8)	0.295
Social functioning	–8.1 (–15.3, –1.0)	0.026	–5.1 (–12.5, 2.2)	0.174
Role emotional	–2.0 (–9.5, 5.4)	0.59	–2.3 (–10.0, 5.4)	0.553
Mental health	0.64 (–3.8, 5.1)	0.78	–1.2 (–5.9, 3.4)	0.604

Values in parentheses are 95 per cent confidence intervals. The analysis included only patients who completed at least one Short Form 36 questionnaire (laparoscopic, 127; open, 143). Values were estimated by a linear mixed model.