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Background: Surgical resection of colorectal liver metastases (CRLMs) is the standard of care when possible, although this strategy has not been compared with non-operative interventions in controlled trials. Although survival outcomes are clear, the cost-effectiveness of surgery is not. This study aimed to estimate the cost-effectiveness of resection for CRLMs compared with non-operative treatment (palliative care including chemotherapy).

Methods: Operative and non-operative cohorts were identified from a prospectively maintained database. Patients in the operative cohort had a minimum of 10 years of follow-up. A model-based cost–utility analysis was conducted to quantify the mean cost and quality-adjusted life-years (QALYs) over a lifetime time horizon. The analysis was conducted from a healthcare provider perspective (UK National Health Service) in a secondary care (hospital) setting.

Results: Median survival was 41 and 21 months in the operative and non-operative cohorts respectively ($P < 0.001$). The operative strategy dominated non-operative treatments, being less costly (€22 200 *versus* €32 800) and more effective (4.017 *versus* 1.111 QALYs gained). The results of extensive sensitivity analysis showed that the operative strategy dominated non-operative treatment in every scenario.

Conclusion: Operative treatment of CRLMs yields greater survival than non-operative treatment, and is both more effective and less costly.

+A: Introduction

Colorectal cancer is one of the commonest malignant diseases worldwide[1] and 30–40 per cent of patients develop colorectal liver metastases (CRLMs)[2,3]. Without treatment the median survival amongst historical patient cohorts with CRLMs suitable for resection was 6–12 months[4,5]; the use of novel chemotherapeutics can extend median survival to 21 months[6]. When possible, resection of CRLMs is associated with a 5-year survival rate of 27–39 per cent[7–10], although with patient cohorts having follow-up for 10 years it is now clear that 5-year survival does not define cure following CRLM resection. Between 11 and 23 per cent of 5-year survivors subsequently develop recurrent metastatic disease, and episodes of recurrence reach a plateau by 10 years[11–13]. Thus 10 years of follow-up are required to identify all disease-specific outcomes following the initial treatment of CRLMs.

The development of surgical resection as a widely adopted treatment for CRLMs was a paradigm change in the management of metastatic disease, and is one of the most exciting advances in surgical practice in recent times. However, in an era of financial austerity and expanding healthcare costs, the financial burden of treating patients with CRLMs is not known. There are barriers to understanding the cost-effectiveness of surgical resection of CRLMs compared with alternative therapies: there is no randomized clinical trial available; an extensive period of follow-up is required to identify all cancer-related outcomes in the surgery group and, therefore, costs; a comparator non-operative group selected from non-randomized cohorts is likely to be disadvantaged owing to selection bias (having more patients with widespread metastatic disease or those unfit for surgery); and novel chemotherapeutic agents continue to be developed which increase survival but are likely to be associated with increasing costs[14–17].

This study used observational data from two separate patient cohorts to undertake a model-based economic evaluation that examined the cost-effectiveness of surgery compared with non-

operative treatment for patients with CRLMs. The results are presented in terms of cost per additional quality-adjusted life-year (QALY) gained.

+A: Methods

The data used in this cost–utility analysis were from an observational study of two patient cohorts. The operative cohort consisted of patients with a minimum of 10 years' potential follow-up in order to capture all episodes of disease recurrence and outcomes. The non-operative cohort was selected carefully to control for selection bias in a number of ways. First, as chemotherapy regimens have evolved to include oxaliplatin and irinotecan[18,19] and, more recently, monoclonal antibodies[20–22], a contemporary patient cohort was used as the comparison group to reflect the improvement in median survival associated with these treatments. Second, to avoid including patients with a prognosis adversely affected by metastatic disease burden or co-morbidity, only those considered fit enough for liver surgery and with liver-only metastatic disease were included in the non-operative cohort. The decision that these patients could not safely undergo surgery was made at a dedicated liver surgery multidisciplinary team meeting. Disease was considered unresectable when: resection of all CRLMs would not leave an adequate volume of future liver remnant; and resection was not technically possible, owing to tumours located at the portal bifurcation or the confluence of the hepatic veins.

The operative cohort comprised consecutive patients undergoing CRLM resection between 28 December 1992 and 24 September 2001, and entered into a prospectively maintained institutional database at St James's University Hospital, Leeds, UK. The outcome of this cohort has been described in detail previously when comparing the ability of scoring systems to predict long-term oncological outcomes[23]. The start of the study coincided with the inception of the liver resection programme at this institution, and the end date permitted a minimum of 10 years actual follow-up for each patient. To provide an accurate assessment of the cost and outcome of treating patients with CRLMs, all patients were included in the present study, including those who died after surgery; such postoperative deaths were excluded in previous reports of 10-year follow-up after surgical resection of CRLM[11,24].

Following liver resection all patients received intensive surveillance consisting of CT of the thorax, abdomen and pelvis at 3, 6, 12, 18 and 24 months, then in years 3, 4, 5, 7 and 10. In addition,

a clinical review with tumour marker measurement (carcinoembryonic antigen, CEA), routine haematology and biochemical analysis was carried out at 3, 6, 12, 18 and 24 months, then annually until the tenth year of follow-up; there was no further review after this. As a result of this intensive surveillance, all episodes of disease recurrence together with outcomes and treatments were recorded. If a patient underwent resection of hepatic or extrahepatic recurrent disease, surveillance was restarted at the beginning of the protocol. Survival data including causes of death were obtained from hospital records, by discussion with individual patients' general practitioners, and by cross-referencing these data with those held by the Northern and Yorkshire Cancer Registry Information Service.

The non-operative cohort was identified from a review of patients who were presented to a dedicated liver surgery multidisciplinary team between January 2008 and January 2010, as described above. For each patient the various chemotherapy regimens and number of cycles administered were recorded. The outcome and costs associated with treating this cohort were directly compared with those in the surgery group. The number of episodes of palliative chemotherapy and survival time from multidisciplinary team review until death were calculated for each patient.

+B: Cost and resource use data

For each subject, costs of investigation, follow-up and treatment were calculated based on Healthcare Resource Groups (HRGs). HRG4 is the current standard in the UK used by the National Health Service (NHS). HRGs are adjusted to reflect case mix, and are based on direct, indirect and overhead costs associated with each reference cost that is measured. Each HRG code considers an individual's age, sex, co-morbidity, primary and secondary diagnoses (using the World Health Organization ICD-10 classification) and primary procedure codes (OPCS version 4.6). The incidence and nature of postoperative complication(s) were also taken into account.

The following costs were calculated. For the operative cohort, the costs of index liver resection and any further resection of hepatic or extrahepatic recurrent disease (including radiofrequency ablation) were considered. Costs of follow-up as described above were also incorporated, which included costs associated with outpatient clinical review, blood tests (full blood

count, routine biochemistry and CEA analysis) and surveillance imaging (CT of 3 body regions with contrast; MRI [when performed to review indeterminate lesions] of 1 body region); and palliative treatment including chemotherapy informed by outcomes of the regimens used in the non-operative cohort.

For the non-operative cohort, the costs of each chemotherapy regimen and the number of cycles provided, along with the number of follow-up appointments and CT or MRI scans, were recorded for each patient.

Cost analysis was based on NHS reference costs for healthcare provided in the 2010–2011 financial year[25] and converted from pounds sterling to euros (€1.26 = £1; exchange rate 21 November 2014). The resource use data for the analysis were based on the experience of the patients in the two cohorts (*Table 1*). The Mann–Whitney *U* test was used for analysis of continuous data and Fisher's exact test for categorical data. Survival analysis was done using the Kaplan–Meier method. All analyses were performed using SPSS version 19 (IBM, Armonk, New York, USA), and $P < 0.050$ was considered statistically significant.

+B: Economic model

+C: Model structure

The model used in this study was developed through consultation with the clinical team using key clinical and modelling expertise. A Markov model was implemented in TreeAge Pro 2001 software (TreeAge Software, Williamstown, Massachusetts, USA). This approach was deemed to be most appropriate owing to the chronic nature of colorectal cancer and there being examples of the same event occurring multiple times over the time horizon of the study (such as a patient experiencing cancer recurrence many years into the future). Because of the reduced length of survival for this patient group, and the possibility of relevant events occurring for the remainder of their lives, a lifetime time horizon for the model was adopted. A weekly time cycle was used in order to capture the increased costs of an inpatient stay after surgery,

For the operative arm, all patients in the model initially undergo surgical resection, and are then followed over time. These patients may suffer a cancer-related death, cancer recurrence or die from natural causes at some stage in the future. For those with cancer recurrence, the immediate response will be either to undertake another surgical resection (hepatic or extrahepatic), or they may be judged to be inoperable, in which case they may or may not go on to receive chemotherapy for the remainder of their lives. The Markov model for the operative pathway is shown *Fig. S1* (supporting information). Patients in the non-operative arm in the model either receive chemotherapy or not, and remain in these states for the remainder of their lives.

+C: Assumptions and parameterization

The majority of the model parameters and transition probabilities between the states were calculated from the data set and are described in *Tables S1* and *S2* (supporting information). A number of assumptions were necessary to implement a workable model structure. These are described here and in the tables of parameters where appropriate. First, patients in the operative arm who develop a recurrence, and are then deemed inoperable, will become similar to patients in the non-operative arm and thus will incur the same costs after recurrence and experience the same rate of survival as those patients. Second, all chemotherapy costs are evenly distributed throughout the remainder of the patients' lives. Third, costs of palliative treatment among patients in the operative arm who develop recurrent unresectable disease are based on the cost of treating patients in the contemporary non-operative group and not of the actual treatment received. This is because, given the duration of follow-up in the surgical group, almost all palliative chemotherapy was in the form of 5-fluorouracil compounds, and these are cheaper than drugs available to patients within the contemporary cohort. Fourth, the mortality rate and length of stay for resection of extrahepatic procedures is the same as that for hepatic disease. Finally, the age of the patients in both cohorts is 62 years; this assumption was made to avoid bias against the non-operative cohort (median age 65 years). The impact of the ages of the cohorts on the model results was examined during the one-way sensitivity analysis.

+C: Analysis

This economic evaluation used the QALY as the primary outcome measure, which is the preferred measure as recommended by the National Institute for Health and Care Excellence (NICE)[27]. The QALY considers the quality of life (QoL) of patients over time; 1 QALY represents 1 year of perfect health.

No QoL data were available from the complete observational data set, and so it was necessary to parameterize this model with QoL data from secondary data sources. Each of the model states in the Markov model were allocated a QoL value, with patients who are inoperable with and without chemotherapy taking the same QoL values in both the operable and inoperative arms. A proportion of the extrahepatic procedures were video-assisted thoracoscopic procedures and this proportion was factored into the QoL values for patients in this state. The QoL values used in this analysis are described in *Table S3* (supporting information).

At baseline the model estimated the mean costs and effectiveness for each of the treatment strategies. Discounting was applied at 3.5 per cent for costs and outcomes as recommended by HM Treasury[31]. The analysis was conducted from a healthcare provider perspective (UK NHS) as recommended by NICE[27] in a secondary care (hospital) setting. As costs could be incurred throughout the lifetime of the patients, half-cycle correction was applied to both costs and outcomes.

+C: Sensitivity analysis

Probabilistic sensitivity analysis was carried out to examine the impact of uncertainties in the model parameters on the robustness of the model results. Beta distributions were used for all transition probabilities and utility values, with costs being described by normal distributions with their standard error values obtained from bootstrapping (*Table S4*, supporting information).

One-way sensitivity analysis was carried out to provide further insight into the impact of specific parameters on the model results. This examined the impact of varying the assumed age of the patient cohort, varying the time horizon, and removing discounting from the model.

One of the key assumptions in this analysis was that the non-operative cohort in this data set can be reasonably used to represent a group of patients who are offered chemotherapy instead of resection. However, because these patients are inoperable it is likely that their mean colorectal cancer-related death rate will be greater than that for all patients with colorectal cancer. To investigate the impact of this factor on the results of the model, in the one-way sensitivity analysis the colorectal cancer-related death rate for the chemotherapy strategy for those that do or do not receive chemotherapy was reduced by half. By varying the death rate in this way the impact of the improved efficacy of future chemotherapy agents could also be examined.

+A: Results

The median (i.q.r.) survival of the 286 patients in the operative cohort was 41 (17–97) months over a potential median follow-up of 151 months. At final follow-up, 18 patients (6.3 per cent) had died within 90 days or during the hospital admission, 58 (20.3 per cent) were alive and disease-free, 192 (67.1 per cent) had died from the disease, 14 (4.9 per cent) from an unrelated cause, and four (1.3 per cent) were lost to follow-up or had died from an unknown cause. Seventy patients (24.5 per cent) had undergone a total of 105 further hepatic or extrahepatic resections for recurrent disease. Further details of the two cohorts are reported in *Table 1*.

Among the non-operative cohort of 46 patients, median (i.q.r.) survival was 21 (10–29) months over a potential median follow-up of 57 (55–62) months. One patient (2 per cent) was alive with disease 34 months after diagnosis of CRLM; the remaining patients all died from disease. The overall survival rate at 1, 3, 5 and 10 years was 80.9, 54.2, 36.1 and 21.9 per cent respectively in the operative cohort, and 70, 13, 0–2 and 0–2 per cent respectively in the non-operative cohort (the variation at 5 and 10 years in latter group was due to the single survivor) (*Fig. 1*).

In the non-operative cohort the reasons for inoperability were CRLMs at the bifurcation of the portal vein/hilum (14) or inferior vena cava/hepatic vein confluence (8), or a pattern of disease that could not be resected to safely leave an adequate future liver remnant (29). Some patients had more than one reason.

Twelve patients in the non-operative cohort either declined or were not offered palliative chemotherapy. Among the remaining patients, 54 cycles of capecitabine, 55 of intravenous 5-fluoruracil, 144 of oxaliplatin, 96 of irinotecan, 52 of cetuximab, and eight of bevacizumab or panitumumab were administered. Various combinations of these drugs were given; the cost analysis was based on the actual regimen received by each patient and the NHS tariff associated with that regimen and route of delivery (*Table 2*).

+B: Cost-effectiveness of treatments

Taking the parameters at their baseline values, the operative strategy was both cheaper and more effective than the non-operative strategy (*Table 3*).

+C: Sensitivity analysis

The results of the probabilistic sensitivity analysis are shown in the cost-effectiveness plane (*Fig. 2*). This indicates that in the majority of patients the operative strategy is both more effective and less costly than the non-operative strategy (majority of points in the south-east quadrant of the cost-effectiveness plane). A number of points lie in the north-east quadrant indicating that the operative strategy is more expensive and more effective than non-operative treatment; the few points in the south-western quadrant indicate the possibility that surgery may be less costly and less effective than non-operative treatment. It is interesting to note that, when allowing for the uncertainty in model parameters, the operative strategy was never found to be more expensive and less effective than the non-operative strategy.

Fig. 3 shows the cost-effectiveness acceptability frontier generated from the results of the probabilistic sensitivity analysis. This indicates that the operative approach is always likely to be the optimal strategy across all willingness-to-pay values for a QALY, and is certain to be the preferred strategy at willingness-to-pay values for a QALY of €6000 or greater.

+C: One-way sensitivity analysis

The results of various one-way sensitivity analyses show that varying the assumed age of the cohorts, the time horizon, and removing discounting from the model all have very little impact on the results or conclusions drawn from the model (*Table 3*). Excluding the 18 postoperative deaths, the median (i.q.r.) survival in the operative cohort increased to 43 (20–111) months, and excluding the 12 patients who received no chemotherapy increased median survival in the non-operative cohort to 24 (14–33) months. The effects of these exclusions in isolation have very little impact on the results or conclusions drawn from the model, and in combination the conclusions from the model remain unchanged. Interestingly, reducing the death rates for the non-operative pathway by half increases the QALY gain for this strategy, but this is still far below that of the operative pathway.

Two models were included to disadvantage the operative cohort and render this more comparable to the palliative nature of the non-operative cohort. The first was to exclude all survivors from the surgical cohort and thus include only patients who ultimately had a cancer-related death. The second was to include only patients with involved surgical margins or those with tumours within 1 mm (R1 resection). Both scenarios remain less costly and yielded greater QALYs than non-operative treatment.

+A: Discussion

This study describes data from an observational study of two patient cohorts, which was then applied to a full economic model to estimate the cost-effectiveness of operative management of CRLMs compared with non-operative management. In analyses of overall survival in non-randomized prospective cohorts, the superiority of liver resection over non-operative treatment in patients with resectable disease was overwhelming[11–13,18–22]. The present study demonstrates that surgical treatment of CRLMs yields a much greater duration of survival together with a chance of cure, despite being associated with a lower cost than palliative treatment based on chemotherapy. The results from the economic evaluation indicate that, using the QALY as outcome measure, the strategy in which all patients with CRLMs undergo surgery is both less costly and more effective than offering all patients non-operative treatments in the form of chemotherapy.

The conclusions drawn from the present economic analysis were also found to be robust to changes to key parameters in the model. The age of the cohort, the time horizon of the analysis, and even changes to the death rate of patients in the non-operative arm had no effect on the conclusions drawn. The operative strategy continued to be both less costly and more effective than non-operative treatment. Moreover, exclusion of postoperative deaths and patients who received no chemotherapy in the non-operative cohort also had very little impact on the results or conclusions. The operative strategy remained dominant compared with non-operative treatment when it was adjusted to become essentially a palliative procedure, that is when only those patients with an involved surgical margin (R1) were included or even when all 10-year survivors were excluded from the analysis.

Furthermore, varying all the parameters in probabilistic sensitivity analysis showed that operative management is certainly the preferred strategy for willingness-to-pay values per QALY of €6300 and above, which is well below the NICE acceptance threshold of €25 200–37 800[32].

The present study has several limitations. The time over which the cohort undergoing surgical resection was observed to accurately identify all relevant outcomes, and thus enable accurate cost efficacy, spans an interval during which chemotherapy regimens evolved considerably in terms of efficacy and costs. Thus an attempt was made to identify all pertinent outcomes and treatment/surveillance interventions in both cohorts to provide an accurate cost-effectiveness assessment. Had the non-operative cohort been selected at the same time as the operative cohort underwent initial liver resection, the chemotherapy drugs and outcomes would not be relevant to contemporary treatment. It could be argued that by excluding contemporary patients undergoing operative treatment the costs associated with laparoscopic liver resection have been neglected and so a more contemporary cohort is required to assess cost-effectiveness. However, it seems unlikely that this strategy would affect survival time and so the costs of alternative surgical treatments can be investigated easily within such a Markov model. The same applies to robotic surgery, if it is assumed that disease-free and disease-specific survival are not affected.

The operative cohort represents a large number of consecutive patients without exclusion; only 1.4 per cent were lost to follow-up or had an uncertain cause of death. Furthermore, the minimum of 10 years' potential follow-up adds confidence to the conclusions drawn from the economic model. However, to compare the efficacy of this treatment, the non-operative cohort was selected carefully to allow comparison of outcomes of the two treatments in a similar group of patients. The two most common reasons why patients with metastatic colorectal cancer do not undergo liver resection of CRLMs are widespread extrahepatic metastases and advanced age/co-morbidity. These patients were excluded from the non-operative cohort in an attempt to avoid disadvantaging this group. Only patients with liver-only metastatic disease and in whom liver surgery would be considered were included in the non-operative cohort. This group is still likely to be disadvantaged compared with the operative cohort given that the burden of hepatic disease precluded resection. However, in other respects the operative group was potentially disadvantaged as patients with extrahepatic disease at the time of liver resection were not excluded from the present study. Without a randomized trial, studies comparing operative and non-operative treatments will always be open to selection bias/confounding. The model parameters were adjusted to benefit the non-operative cohort by excluding patients who did not receive chemotherapy and by assuming improved efficacy of future chemotherapeutic agents. An analysis was also done with exclusion of all survivors in the operative cohort to give essentially a palliative group of operated patients, but the outcome remained the same with operative treatment being more cost-effective in every scenario.

A further assumption in this analysis was that chemotherapy costs are distributed evenly over a patient's lifetime. In reality it is likely that these patients will stop receiving chemotherapy towards the end of their lives. In terms of the present analysis, this means that the costs in the non-operative arm may be higher than estimated here, as discounting will have less of an impact if the costs are incurred sooner. This helps increase confidence in the conclusion that offering resection to all patients with colorectal cancer is both less costly and more effective than offering chemotherapy instead.

One conclusion of this work is that the standard of care should be liver resection in patients who are fit for surgery, and have resectable hepatic metastases and no extrahepatic disease. This is

based on improved survival, QoL and cost-effectiveness analysis. It can be concluded from the results here that strategies to identify early disease recurrence and increase the proportion of patients undergoing liver resection may make financial sense if the costs of identifying these patients are not prohibitive. Presently there is worldwide concern that some patients with resectable CRLMs are not referred for specialist review[33]. Furthermore, strategies to increase the proportion of patients with CRLMs who can undergo resection, such as two-stage liver resections[34], portal vein embolization[35] and downstaging chemotherapy[26], should be supported as they are likely to be financially worthwhile endeavours. This study has clearly put into a financial context the position of surgery against other treatments. This information is particularly useful for financially constrained healthcare systems to inform where funding may be most usefully allocated.

The QoL estimates in this analysis were taken from a number of secondary sources, some of which are a number of years old. As treatment practices improve, it is likely that these will have less of an impact on patients' QoL, and also help to prolong their survival. Recovery from operative procedures may be improving, and the side-effects from new chemotherapy drugs may be less severe than those of agents used in the past.

Other potentially curative treatments for CRLMs include ablation therapies (percutaneous or intraoperative) and minimally invasive techniques, although these were not reviewed for the present study. These treatments could also improve QoL outcomes[28]. Given that there is no evidence to suggest that the recurrence rate after ablation[29] or laparoscopic surgery[30] is higher than that after open surgery, these strategies could further improve the delivery of curative treatments in selected patients.

Chemotherapy is now being used to improve oncological outcomes after CRLM resection[36] and increasingly to bring initially unresectable disease to a state where liver resection is possible[37]. These issues further complicate any future cost-effectiveness analyses, and demonstrate the close relationship between surgeons, oncologists and their patients. Therefore, future research could investigate the impact of current practice on QoL, and the present analysis could then be updated based on this new information.

+A: Disclosure

The authors declare no conflict of interest.

+A: References

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Model parameters (Word document)

Table S2 Transition probabilities used in the Markov model at baseline (Word document)

Table S3 Utility values used in the Markov model (Word document)

Table S4 Distributions used in the probabilistic sensitivity analysis (Word document)

Fig. S1 Structure of Markov model for operative strategy

Fig. S2 Scatter plots and cost-effectiveness acceptability curves for the probabilistic sensitivity analysis, assuming that: **a**,**b** there are no postoperative deaths following initial resection in the operative pathway; **c**,**d** all patients in the non-operative pathway receive chemotherapy; **e**,**f** there are no postoperative deaths following initial resection in the operative pathway and all patients in the non-operative pathway receive chemotherapy; and **g**,**h** all patients in the operative pathway have involved surgical margins (Word document)

Fig. S3 Scatter plot and cost-effectiveness acceptability curve for the probabilistic sensitivity analysis assuming that there were no survivors at 10 years in the operative pathway (Word document)

Fig. 1 Survival curves for operative and non-operative cohorts. Only patients who had non-cancer non-postoperative deaths were censored in the operative cohort. One patient who was alive was censored in the non-operative cohort. Median survival was 21 (i.q.r. 10–29) and 41 (17–97) months for the non-operative and operative cohorts respectively ($P < 0.001$, Cox regression analysis). The effects of including only those who received chemotherapy in the non-operative cohort, and excluding all early postoperative deaths in the operative cohort, are also shown

Fig. 2 Scatter plot showing the results of probabilistic sensitivity analysis for baseline parameters. QALY, quality-adjusted life-year

Fig. 3 Cost-effectiveness acceptability frontier across a range of willingness-to-pay thresholds for a quality-adjusted life-year (QALY)

Table 1 Summary of the cohort undergoing operative and non-operative treatment for colorectal liver metastases, including pathological features of colorectal and hepatic tumours, hepatic surgery and outcomes

	Operative cohort (n = 286)	Non-operative cohort (n = 46)	P§
Age (years)*	62 (54–69)	65 (56–74)	0.186¶
Sex ratio (M : F)	170 : 116	28 : 18	0.920
Synchronous CRLMs	132 (46.2)	19 (41)	0.680
Extrahepatic disease at time of diagnosis of CRLMs	27 (9.4)	0 (0)	0.061
Adjuvant chemotherapy of CRC	86 (30.1)	30 (65.2)	< 0.001
N1 primary CRC	157 (54.9)	31 (67.4)	0.140
T4 primary CRC	90 (31.5)	8 (17.4)	0.081
Interval between CRC and CRLM operations (days)*	290 (132–651)	405 (130–885)	0.627¶
Bilobar disease	127 (44.4)	32 (70)	0.002
No. of CRLMs*†	2 (1–4)	4 (3–6)	< 0.001¶
Size of largest CRLM (cm)*	4 (2.6–6)	4 (3–5.3)	0.574¶
Complications	81 (28.3)	–	
Further resection for CRC metastases	70 (24.5)	–	
Follow up (months)*	151 (133–179)	57 (55–62)	< 0.001¶
Survival (months)*	41 (17–97)	21 (10–29)	< 0.001¶
Follow-up appointments*	6 (3–13)	26 (10–36)	< 0.001¶
Follow-up CT (no. of scans)*	10 (5–19)	4 (2–6)	< 0.001¶
Follow-up MRI (no. of scans)*	6 (3–13)	1 (0–1)	< 0.001¶
Outcomes at final follow-up			
Alive, disease-free	58 (20.3)	0 (0)	0.002
Alive, with disease	0 (0)	1 (2)	0.292
Died from disease	192 (67.1)	45 (98)	< 0.001
Died in early postop. phase	18 (6.3)	–	
Died from an unrelated cause	14 (4.9)	0 (0)	0.258
Died from an unknown cause	3 (1.0)	0 (0)	0.887
Lost to follow-up	1 (0.3)	0 (0)	0.292
Crude survival			
1 year	80.9	70	
3 years	54.2	13	
5 years	36.1	0–2	
10 years‡	21.9	0–2	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Number of lesions in the surgical resection specimen or identified at staging imaging in the non-operative cohort. ‡Median follow-up for non-operative cohort does not exceed 5 years. CRLM, colorectal liver metastasis; CRC, colorectal cancer; N1, node-positive; T4, tumour breaches serosal wall. §Fisher's exact test, except ¶Mann–Whitney U test.

Table 2 Resource use costs applied to economic evaluation

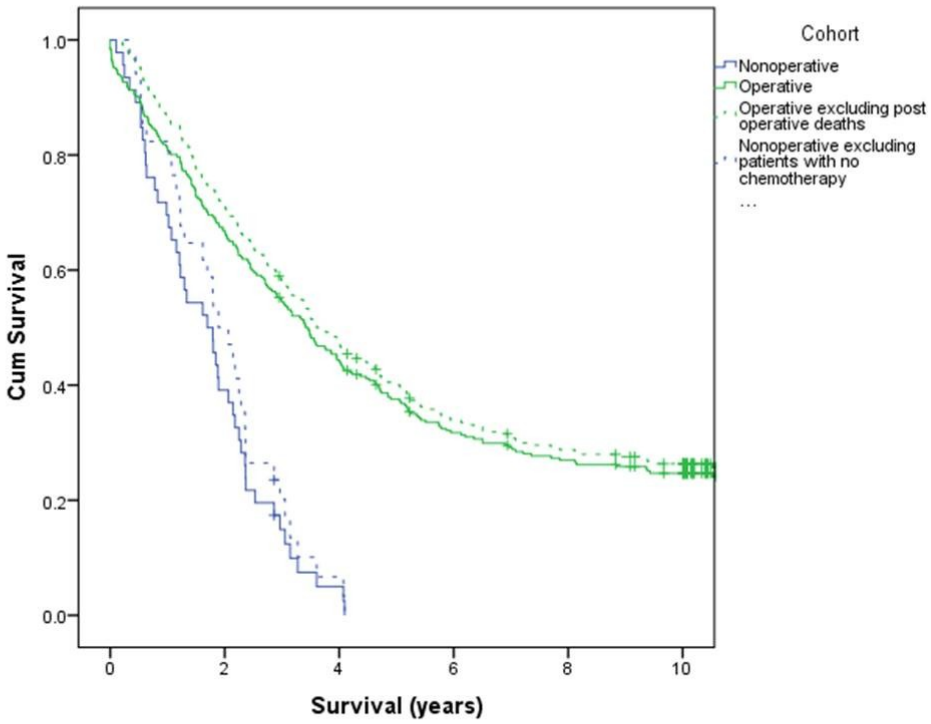
	Code*	Cost (€)	Reference for cost	notes
Resection procedure	GA03A, GA03B, GA04A, GA04B, GA05A, GA05B	€7132.1 (93.7)	NHS reference costs	Bootstrapped from observational data to obtain mean and s.e.
1-week postop. hospital stay		2886.6 (25.1)		Mean length of stay 11.4 days
Extrahepatic operation	DZ02C		NHS reference costs	Bootstrapped from observational data to obtain mean and s.e.
Procedure		5278		
One-week hospital stay		3501		Mean length ofstay assumed to be same as for resection
Chemotherapy	SB01Z-SB17Z, SB97Z	Mean weekly cost €429 (64.8)	NHS reference costs	Bootstrapped from observational data to obtain mean and s.e. Includes day-case and regular day/night appointments and outpatient visits. It is assumed that the chemotherapy costs are distributed evenly over time
Outpatient appointments	315	260	NHS reference costs	Assume four appointments in the first year postop. and one per year afterwards
CT	RA13Z	204	NHS reference costs	Two scans in the first year postop.; one per year subsequently
MRI	RA05Z	461	NHS reference costs	
Inoperable patients		92.7 (weekly cost)		0.3 appointments per week, 0.0467 CT scans per week, 0.0115 MRI scans per week, based on observational data

Values in parentheses are s.e. *National Health Service (NHS) reference costs.

Table 3 Results of one-way sensitivity analysis

Strategy	Cost (€)	Effectiveness (QALYs gained)	Cost-effectiveness
Baseline			
Non-operative	32 800	1.111	
Operative	22 200	4.017	Dominates
Assume all patients are aged 45 years			
Non-operative	33 300	1.125	
Operative	23 000	4.249	Dominates
Assume all patients are aged 75 years			
Non-operative	31 100	1.055	
Operative	20 300	3.392	Dominates
Time horizon limited to 10 years			
Non-operative	32 700	1.106	
Operative	20 600	3.533	Dominates
No discounting			
Non-operative	35 100	1.183	
Operative	24 400	4.793	Dominates
Reduce non-operative pathway death rates by half			
Non-operative	60 400	2.052	
Operative	22 200	4.017	Dominates
Assume no postoperative deaths following initial resection in the operative pathway*			
Non-operative	32 900	1.111	
Operative	22 800	4.208	Dominates
Assume all patients in non-operative pathway receive chemotherapy*			
Non-operative	42 800	1.289	
Operative	22 200	4.017	Dominates
Assume no post-operative deaths following initial resection in operative pathway and all patients in non-operative pathway receive chemotherapy*			
Non-operative	42 800	1.289	
Operative	22 800	4.208	Dominates
Assume no survivors in operative pathway; all 10-year survivors excluded from analyses†			
Non-operative	32 900	1.111	
Operative	14 200	3.563	Dominates
Assume all patients have involved surgical margins; all patients with R0 resection margins excluded from analyses*			
Non-operative	32 900	1.111	
Operative	22 900	2.802	Dominates

*Results of probabilistic sensitivity analyses can be found in **Fig. S2* and †*Fig. S3* (supporting information). QALY, quality-adjusted life-year.



Numbers at risk											
Nonoperative	46	32	18	6	2						
Nonoperative excluding patients with no chemotherapy	34	28	17	6	2						
Operative	286	232	191	155	126	104	87	79	73	69	63
Operative excluding post operative deaths	268	232	191	155	126	104	87	79	73	69	63

Fig. 1

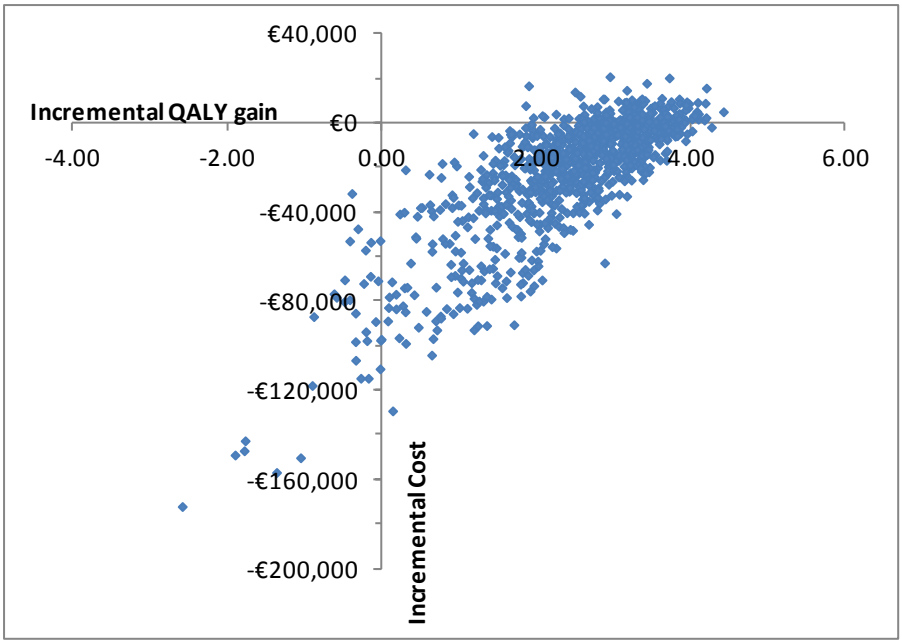

€40,000
Incremental QALY gain
€0
-4.00
-2.00
0.00
2.00
4.00
6.00
-€40,000
-€80,000
-€120,000
-€160,000
-€200,000
Incremental Cost

Figure 2:

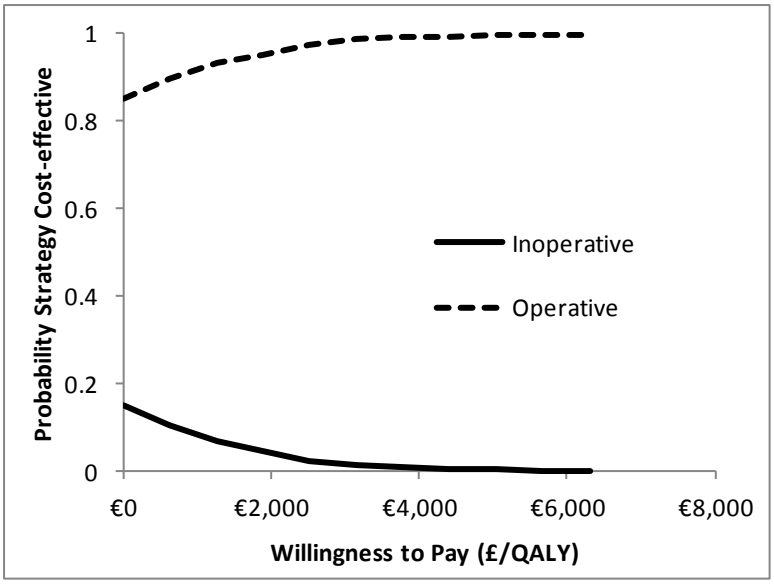

1
0.8
0.6
0.4
0.2
0
Probability Strategy Cost-effective
Inoperative
Operative
€0
€2,000
€4,000
€6,000
€8,000
Willingness to Pay (£/QALY)

Fig. 3