European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Ablation versus resection for resectable colorectal liver metastases - Health care related cost and survival analyses from a quasi-randomised study

Pascale Tinguely [a], Gustaf Laurell [a], Anton Enander [a], Jennie Engstrand [b, *], Jacob Freedman [a]

[a] Division of Surgery, Department of Clinical Sciences, Karolinska Institutet at Danderyd Hospital, Stockholm, Sweden
[b] Division of Surgery, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, 141 86, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 8 August 2022
Received in revised form
7 September 2022
Accepted 7 September 2022
Available online xxx

Keywords:
Liver
Neoplasm metastasis
Ablation techniques
Hepatectomy
Healthcare costs
Survival analysis

ABSTRACT

Background: The aim of this study was to compare healthcare related costs and survival in patients treated with microwave ablation (MWA) versus surgical resection for resectable colorectal liver metastases (CRLM), in patients from a quasi-randomised setting.
Methods: The Swedish subset of data from a prospective multi-centre study investigating survival after percutaneous computer-assisted Microwave Ablation VErsus Resection for Resectable CRLM (MAVERRIC study) was analysed. Patients with CRLM ≤ 3 cm amenable to ablation and resection were considered for study inclusion only on even calendar weeks, while treated with gold standard resection every other week, creating a quasi-randomised setting. Survival and costs (all inpatient hospital admissions, outpatient visits, oncological treatments and radiological imaging) in the 2 years following treatment were investigated.
Results: MWA (n = 52) and resection (n = 53) cohorts had similar baseline patient and tumour characteristics and health care consumption within 1 year prior to CRLM treatment. Treatment related morbidity and length of stay were significantly higher in the resected cohort. Overall health care related costs from decision of treatment and 2 years thereafter were lower in the MWA versus resection cohort (mean ± SD USD 80′964±59′182 versus 110′059±59′671, P < 0.01). Five-year overall survival was 50% versus 54% in MWA versus resection groups (P = 0.95).
Conclusions: MWA is associated with decreased morbidity, time spent in medical facilities and healthcare related costs within 2 years of initial treatment with equal overall survival, highlighting its benefits for patient and health care systems.

1. Introduction

Thermal ablation using radiofrequency or microwave techniques is a low morbidity treatment alternative to surgical resection for colorectal liver metastases (CRLM). Its parenchyma-sparing aspect and easy applicability by minimally invasive treatment accesses lower major complication rates to around 8%, and shortens or eliminates in-hospital stay [1]. This further allows multiple retreatments in case of hepatic CRLM recurrence, occurring in 71% of patients treated for CRLM, regardless of the type of initial treatment [2]. Regarding oncological outcomes, data from well-powered randomised clinical trials (RCT's) investigating non-inferiority compared to surgical resection are still lacking, with ongoing trials being delayed in patient inclusion. Alternative trial designs such as population-based analyses adapting for selection bias confirm similar survival rates of around 70% and 50% after 3 and 5 years [3–5], and thermal ablation was incorporated into current guidelines as a first line treatment for oligometastatic CRLM [6].

Decreased morbidity, shortened length of hospital stay and similarity in oncological outcomes suggest that thermal ablation for CRLM might be beneficial to the health care system also in terms of

* Corresponding author.
E-mail address: jennie.engstrand@ki.se (J. Engstrand).

https://doi.org/10.1016/j.ejso.2022.09.006
0748-7983/© 2022 Published by Elsevier Ltd.

costs. Previous studies investigating cost effectiveness of thermal ablation compared to surgical resection based on model parameters suggest that thermal ablation might indeed be a cost effective [7–9]. However, data comparing health care related costs after thermal ablation versus surgical resection from clinical data with patients amenable to both ablation and resection are currently lacking.

The aim of this study was to analyse health care related costs and overall survival in patients treated with thermal ablation versus surgical resection for CRLM amenable to both ablation and resection, in a Swedish patient cohort arising from a quasi-randomised study design within a larger international multicentre study (MAVERRIC).

2. Materials and methods

2.1. Study population

The MAVERRIC trial (Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases) is an ongoing European multicenter prospective cohort study aiming to prove oncological non-inferiority (primary outcome: 3-year overall survival) of microwave ablation (MWA) versus surgical resection for curative-intent treatment of CRLM [10]. In this trial, patients with $\leq$5 CRLM of $\leq$30 mm, amenable for both surgical resection and percutaneous computed tomography (CT)-guided stereotactic MWA as decided by the local liver multidisciplinary team (MDT) conferences, were deliberately treated with percutaneous MWA. Patients with previous MWA for CRLM were excluded. Outcomes from the study group will be compared with results from a cohort of patients after surgical resection for CRLM extracted from a population-based patient registry [11]. Between December 2015 to November 2018, three recruiting tertiary liver centres in Stockholm Sweden, Groningen Netherlands and Bern Switzerland prospectively included 98 patients.

For the current analysis, the subgroup of patients included in the MAVERRIC trial in Stockholm Sweden was extracted and analysed separately. In this specific subgroup, patients were prospectively considered for inclusion into the MAVERRIC study only every second week, i. e. on even calendar weeks (MWA cohort). On odd calendar weeks, patients were not considered for inclusion into the MAVERRIC trial and were treated with surgical resection as per the current gold standard for treatment of CRLM (resection cohort). Patients theoretically meeting the inclusion criteria for the MAVERRIC trial on these weeks (i.e., both amenable to percutaneous MWA and surgical resection) and treated with resection were nevertheless prospectively registered in an anonymised data sheet. This particular inclusion pattern led to the formation of two prospective cohorts with a quasi-randomised setting, opening opportunities for outcome analyses. Fig. 1 shows the inclusion process and cohort selection. Ethical approval was obtained for the spin-off study from the MAVERRIC trial from the local ethics review board (2015/1453-31/4 and 2020-00787).

2.2. Treatment strategy and follow-up

Percutaneous stereotactic CT-guided MWA procedures were performed by multidisciplinary teams of surgeons and radiologists, with the primary responsibility being under the surgery department. The procedure has been described in detail previously [12,13]. In brief, CRLM were treated with local thermal ablation (microwave energy at 2,45 MHz), aiming to locally destroy all tumour tissue. Patients were under general anaesthesia and ventilated with high frequency jet ventilation to minimise breathing related liver motion to enhance the stereotactic treatment [14]. Ablation planning and stereotactic tumour targeting were performed using the CAS-one system (CAScination AG, Bern, Switzerland). Immediate post-interventional review overlay of pre- and post-ablation CT images allowed review of the completeness of the tumour ablation, with possibility of immediate re-ablation if necessary [13]. Patients were kept in hospital until pain levels were manageable with oral agents, food intake assured and urinary output secured. Radiological follow-up included liver CT or magnetic resonance imaging (MRI) every 3 months for the first year and every 6 months in the two following years (Fig. 1). No synchronous MWA and resection of the colorectal primary tumour was performed in the MWA cohort, since CT-guided ablations in the OR-suite was not an available option.

Surgical resection was performed as per local guidelines and standards of care at the Karolinska University Hospital in Stockholm Sweden, which is a tertiary referral centre for Hepato-Pancreatico-Biliary surgery. A laparoscopic or open access was used, with the goal of minimising surgical trauma and loss of liver parenchyma. No combined resection and ablation was performed in the studied cohorts. Patients were discharged to specialised rehabilitation units for prolonged rehabilitation care when appropriate as per the local standards. Radiological follow-up included liver CT or MRI every 6 months for the first two years and yearly imaging thereafter (Fig. 1).

2.3. Data collection

Baseline characteristics of patients, the primary colorectal cancer and of CRLM at the time of the index liver treatment (MWA or surgical resection) were extracted from patients' medical records. The appearance of CRLM was defined as synchronous if the diagnosis of CRLM was made prior to or during surgery for the primary colorectal tumour [15]. Complications related to the index treatment were classified according to Clavien-Dindo [16]. Intrahepatic recurrences and re-interventions, recurrence of primary tumour and distant metastases arising during follow-up were extracted.

To investigate baselines in patients' health care use, health care consumption (number and type of outpatient visits for any medical reason, number of inpatient hospital admissions for any medical reason) were collected for a time 12 months prior to patient inclusion at the liver MDT. Overall health care consumption was further collected from the time of patient inclusion at the liver MDT for 24 months onwards, including the index liver treatment. These included the number of primary tumour related outpatient visits to oncologists and surgeons, number of inpatient days for any hospital admissions, number of MDTs, diagnostic imaging for CRLM using CT, MRI or positron emission tomography-CT (PET-CT), number and kind of oncological treatments received (chemotherapy and radiotherapy). Cost data was collected in Swedish Crowns and converted into United States Dollars (USD) using the average conversion rate during the study period of patient inclusion.

Total costs were calculated from patient inclusion at the liver MDT and 24 months onwards, including all inpatient admissions for any medical reason during this time period, outpatient visits (surgery, oncology or palliation team) related to the colorectal cancer disease, all radiological imaging related to the colorectal cancer disease (CT, MRI and PET), oncological treatments (chemotherapy and radiotherapy) related to the colorectal cancer disease and costs for MDT conferences related to the colorectal cancer disease.

Costs for inpatient hospital admissions were obtained using Diagnosis-Related Group (DRG) and Cost Per Patient (CPP) measures. DRG is an international system for classifying patient visits to health care centres into groups of homogenous medical character and resource consumption, based on main diagnosis, secondary diagnoses, interventions performed, complications, age, time spent

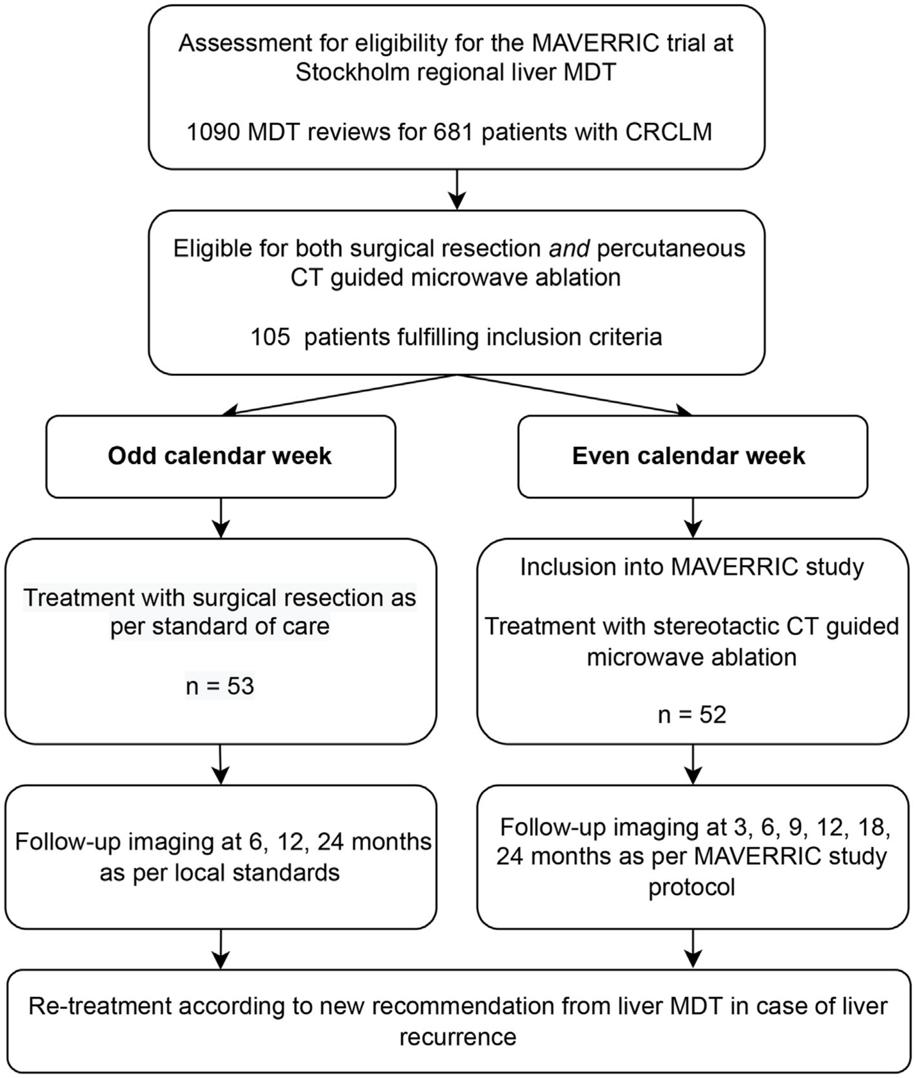

Fig. 1. Flow chart illustrating the inclusion process, study cohorts and follow-up strategy. MAVERRIC, microwave ablation versus resection for resectable colorectal liver metastases; MDT, multidisciplinary team; CRLM, colorectal cancer liver metastases.

at the health centre and mode of discharge. CPP represent the actual cost for each contact with a health care provider in Sweden, including overhead costs. CPP was preferred in the current analyses, when available, since it gives a more precise assessment of actual costs than DRG. For all other occasions the DRG-based costs were extracted. Fixed remunerations reported by some rehabilitation units were used for assigning such inpatient costs.

For outpatient visits, DRG based costs were readily extractable from the electronic medical journal system Take Care (TakeCare, CompuGroup Medical, Stockholm, Sweden).

Costs for radiological imaging, MDT conferences and oncologic treatments were obtained by consulting economists in the different hospitals in the region of Stockholm, and calculated accordingly. The cost of oncological treatments including chemotherapy and radiotherapy was calculated from the costs associated to the administration of one treatment cycle and from the costs of actual drugs used.

2.4. Statistical analyses

Continuous data were analysed as means with standard deviations (SD) and medians with interquartile ranges (IQR), and categorical variables as absolute numbers. Differences between groups were analysed using the Wilcoxon rank-sum test, Pearson's chi-squared test or Fisher's exact test, as appropriate. Survival was defined as the time from index treatment until time of death from any diagnosis. Overall survival (OS) curves were obtained and probability of survival estimated with the Kaplan-Meier method and differences in OS analysed using the Log-rank test and the Wilcoxon (Breslow) test. The assumption of proportional hazards was investigated (testing of Schoenfeld residuals, adding time-dependent interaction term into multivariable Cox model), yielding no evidence against the proportionality of hazards. Factors potentially influencing OS, chosen based on previous knowledge, were investigated using univariable and multivariable Cox proportional hazard models. Factors yielding a p-value of <0.2 in univariable analysis were included into multivariable analyses. The threshold for statistical significance was set to a <0.05. STATA/IC version 15.0 (StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA) was used for all statistical analyses.

3. Results

Between December 2015 and November 2018, 681 patients with

CRLM were reviewed at the Stockholm regional liver MDT conference, of which 105 fulfilled the inclusion clinical criteria for the MAVERRIC trial. This led to inclusion of 52 patients into to the MAVERRIC trial on even calendar weeks, treated with stereotactic CT guided MWA, and 53 patients treated with surgical resection on odd calendar weeks, during the same time period (Fig. 1).

In the cohort of patients undergoing surgical resection for CRLM, 12 (23%) had laparoscopic liver resections, 6 (11%) laparoscopic converted to open resections and the rest were open liver resections. Twenty-seven (51%) were atypical local resections, 14 (26%) were segmental resections, 10 (19%) were right lobectomies and 2 (4%) were left lobectomies as the main resection type. Of the eleven patients treated for bilobar CRLM, 2 had a left lobectomy plus local resections, 3 had a right lobectomy plus local resections and 6 had multiple local and/or segmental resections. Sixteen patients (30%) had synchronous resection of the colorectal primary tumour at the time of CRLM resection, including 11 right hemicolectomies, 3 left hemicolectomies and 2 low anterior resections. Resection margins of the CRLM were negative in all resected liver specimens in 43 (81%) patients. In the MWA cohort, treatment efficacy (patients with no tumour residue at site of ablation at post ablation follow-up imaging at 3 months) was 85%.

Baseline characteristics of MWA and surgical resection cohorts are summarised in Table 1. Patient characteristics including comorbidity, primary tumour and CRLM characteristics, and oncological perioperative chemotherapy regimens were similar in both cohorts. There was no difference in the number of patients undergoing a “liver first” approach, i.e. having the primary tumour in situ at the time of the index liver treatment, in both cohorts. Baseline health care consumption within one year prior to the liver MDT conference were similar, except the number of non-oncology related outpatient visits, which was higher in the MWA cohort. There was no difference in the number of patients having their primary tumour resected within one year prior to the liver MDT conference (Table 2).

Main peri-operative outcomes, *i.e.* health care consumption from liver MDT conference two years onwards, and costs are summarised in Table 2. Patients who underwent surgical resection had significantly more overall complications than the MWA cohort (60% versus 15%). Major complications of Clavien-Dindo grade $\geq$ III in the surgical resection group included two cases of pneumothorax or pleural effusion requiring drainage, seven of perihepatic fluid collections requiring percutaneous drainage, three cases of bile leakage requiring endoscopic drainage and one case of colovesical fistulation requiring re-operation in a case of synchronous resection of the colorectal primary tumour. Of the four patients with simultaneous resection of the primary tumour developing a major complication, only one was associated with the colonic resection. In the MWA cohort, one patient required pleural drainage after a haemothorax. The mortality in the surgical resection cohort was a case of liver failure (small-for-size liver insufficiency exacerbated due to infection) and kidney failure following right hepatectomy and local resections for bilobar CRLM. In the MWA cohort, a patient died on day 21 from a cardiac event after surgical re-intervention due to a liver abscess fistulating into small bowel. No patient required admissions to rehabilitation centres following hospital discharge in the MWA cohort, leading to significantly enhanced rehabilitation admissions and related costs in the surgical resection cohort. While health care consumption was similar, total health care related costs from the liver MDT conference two years onwards were significantly lower in the MWA versus surgical resection cohorts (Fig. 2) (Table 2). The main difference in costs were related to inpatient hospital admissions, including the index treatment admission, which were significantly higher in the surgical resection versus MWA cohort (Table 2).

Median follow-up was 46 (IQR 37–63) months in the MWA cohort and 48 (IQR 30–58) months in the surgical resection cohort. Total liver recurrences of CRLM were 69% in the MWA cohort and 45% in the surgical resection cohort (3-year recurrence-free survival 33% versus 56%, P = 0.014 Log rank test). In the MWA cohort, 27 (52%) patients had 40 further treatments for recurrent CRLM within the first 2 years, of which 36 were re-ablations with percutaneous MWA and 4 were resections. In the liver resection cohort, 14 (26%) patients had 16 further treatments for recurrent CRLM within the first 2 years (two patients had 2 more treatments), of which 13 were surgical resections and 3 were percutaneous ablations.

Any recurrence, including liver, extrahepatic or at primary tumour location, occurred in 32 (60%) of patients in the surgical resection cohort and 40 (77%) in the MWA cohort. Estimated 3-year disease-free survival was 28% in the MWA and 40% in the surgical resection cohorts, 5-year disease-free survival was 22% in the MWA and 37% in the surgical resection cohort (P = 0.150 Log rank test).

Overall survival after index treatment was similar in both cohorts, with estimated 3-year OS of 75% (CI 61–85%) after MWA versus 70% (56–80%) after surgical resection. Estimated 5-year overall survival was 50% (35–64%) after MWA versus 54% (40–67%) after surgical resection (Log rank test P = 0.947, Wilcoxon (Breslow) test P = 0.831) (Fig. 3). Multivariable Cox regression analysis yielded the number of liver metastases at the time of patient inclusion as the only factor significantly influencing overall survival with a HR of 2.4 (CI 1.3, 4.6). The type of index treatment approach (MWA versus surgical resection) had no effect on survival, with a HR of 1.0 (CI 0.6, 1.7) (Table 3).

4. Discussion

This study shows that while treatment with MWA or surgical resection for patients with CRLM lead to similar overall survival, total health care related costs are significantly reduced in the two first years after MWA treatment, with reduced treatment related complications and time spent in hospital. To the best of our knowledge, this is the first study analysing survival and costs from clinical data arising from a quasi-randomised setting, where MWA or surgical resection was allocated based on calendar week number, in patients qualifying for both percutaneous CT-guided MWA and surgical resection. This led to two comparable treatment cohorts with similar baseline patient-, tumour- and health care consumption characteristics.

No data from well-powered RCT's on oncological outcomes are available to date. Several attempts to conduct RCT's on thermal ablation versus surgical resection analysing oncological endpoints have been initialised, but have either been abandoned, or not concluded [17–19]. Reasons for this are based mainly on the large number of trial participants needed when designing clinical trials on meaningful oncological endpoints. The nature of investigated treatments often requires trial designs with involvement of more complex logistics with different medical specialities and clinical units, i.e. surgeons for surgical resection and radiologists for thermal ablation. Also, a transfer of curative treatment from surgery to interventional radiology can cause challenging resource shifting issues. Facing the current lack of data from RCT's, more recent population based analyses show that when adapting for confounders leading to inclusion of healthier patients for surgical resection and more comorbid patients for thermal ablation, long term overall survival is similar [3,5]. This was confirmed in the current analysis using prospective data, with survival rates corresponding to previously published rates of around 70% at 3 years and 55% at 5 years after MWA for potentially resectable CRLM [20] and the type of treatment not influencing survival in multivariable

Table 1
Baseline patient, tumour and treatment characteristics and health care consumption one year prior inclusion for treatment.

	MWA (n = 52)	Resection (n = 53)	P-value
Age (years)[a]			
Median (IQR)	67.5 (IQR 62–77)	66 (IQR 61–72)	0.369[b]
Sex ratio			
Male: Female	33:19	31:22	0.602[c]
ASA class[a]			
I	5	12	0.297[d]
II	26	25	
III	18	13	
IV	3	3	
WHO Performance status[a]			
0	27	33	0.593[d]
1	22	18	
2/3	3	2	
Charlson comorbidity index[a]			
6/7	8	10	0.700[d]
8	13	17	
9	15	16	
10	7	5	
≥ 11	9	5	
Primary tumour location			
Right-sided	20	20	0.939[c]
Left-sided	32	33	
Primary tumour stage (pT)			
0	1	1	0.305[d]
1	1	3	
2	7	6	
3	30	20	
4	13	20	
Unknown	0	3	
Primary tumour nodal stage (pN)			
0	16	14	0.759[c]
1/2	36	36	
Unknown	0	3	
Primary tumour KRAS mutation			
Yes	22	9	0.703[c]
No	30	10	
Unknown	0	34	
Primary tumour perioperative chemotherapy			
None	16	13	0.668[d]
Neoadjuvant only	19	15	
Adjuvant only	15	20	
Neoadjuvant & adjuvant	2	3	
Number of liver metastases[a]			
1	24	29	0.380[c]
2 - 5	28	24	
Bilobar liver metastases[a]			
Yes	11	11	0.960[c]
No	41	42	
Size of largest liver metastasis[a]			
Mean ± SD	15.4±6.1	15.2±6.9	0.905[b]
Previous liver resection[a]			
Yes	5	0	0.027[d]
No	47	53	
Perioperative chemotherapy[a]			
None	32	24	0.398[d]
Neoadjuvant only	3	5	
Adjuvant only	6	7	
Neoadjuvant & adjuvant	11	17	
Primary tumour in situ (”Liver first” approach)[a]			
Yes	23	14	0.546[c]
No	29	23	
Synchronous lung metastases[a]			
Yes	1	5	0.205[d]
No	51	48	
Health care consumption within 1 year prior liver MDT conference			
N outpatient visits oncology related			
Mean ± SD	17.673±20.540	16.240±33.324	0.620[b]
Median, IQR	7.5 (2–33)	7 (3–19)	
N outpatients visits non-oncology related			
Mean ± SD	11.5±16.928	4.792±7.286	0.003[b]
Median, IQR	5 (2–11.5)	2 (IQR 1–6)	
N inpatient admissions			
Mean ± SD	1.365±2.223	1.096±1.524	0.520[b]
Median, IQR	1 (IQR 0–2)	1 (IQR 0–1.5)	

(*continued on next page*)

Table 1 (*continued*)

	MWA (n = 52)	Resection (n = 53)	P-value
Primary tumour resection within 1 year prior to liver MDT conference			
Yes	25	33	**0.144**[c]
No	27	20	

MWA, microwave ablation; ASA, American Society of Anesthesiology; WHO, World Health Organization; SD, standard deviation; IQR, interquartile range; MDT, multidisciplinary team; N, number.
[a] At time of index treatment.
[b] Wilcoxon rank-sum test.
[c] $\chi 2$ test.
[d] Fisher's exact.

Table 2
Peri-operative outcomes, health care consumption and costs from treatment decision and two years onwards.

	MWA (n = 52)	Resection (n = 53)	P-value
Complications after index treatment			
Overall	8	32	<0.001[b]
CDC I & II	6	18	0.001[b]
CDC III a/b, IV a/b	1	13	
CDC V	1	1	
Length of stay after index treatment (days)			
Median, IQR	1 (IQR 0–1)	7 (IQR 5–11)	<0.001[a]
Rehabilitation after index treatment			
Yes	0	24	<0.001[b]
No	52	29	
Health care consumption from liver MDT conference 2 years onwards			
N outpatient visits surgery related			0.064[a]
Mean ± SD	5.235±3.424	6.170±2.940	
Median, IQR	4 (IQR 2.5–8)	6 (IQR 4–8)	
N outpatient visits oncology related			0.298[a]
Mean ± SD	7.5±7.485	6.264±6.870	
Median, IQR	6 (1–11.5)	4 (0–9)	
N inpatient admissions			0.357[a]
Mean ± SD	4.846±3.599	4.226±3.080	
Median, IQR	4 (IQR 3–6)	3 (IQR 2–7)	
N radiological imaging			<0.001[a]
Mean ± SD	11.865±3.302	7.434±2.925	
Median, IQR	12 (IQR 9–14)	8 (IQR 5–9)	
Costs from liver MDT conference 2 years onwards (USD)			
Outpatient visits			0.511[a]
Mean ± SD	6661±4660	6913±4051	
Median, IQR	6248 (2587–9898)	6258 (3254–9470)	
MDT conferences			0.051[a]
Mean ± SD	6056±4662	7492±4630	
Median, IQR	4564 (3043–7607)	6085 (4564–9128)	
Radiological imaging			
Mean ± SD	7777 +/2369	3816±1683	<0.001[a]
Median, IQR	8042 (6679–9524)	3695 (2482–5036)	
Total oncologic treatment			
N patients	31	38	0.279[a]
Mean ± SD	23543±16380	22638±23672	
Median, IQR	17087 (11006–33684)	17087 (7420–22523)	
Chemotherapy related costs			
N patients	31	37	0.310[a]
Mean ± SD	22830±16028	22713±23676	
Median, IQR	17087 (11006–31850)	17087 (7420–20689)	
Radiotherapy related costs			
N patients	9	11	0.232[a]
Mean ± SD	2458±1263	1804±231	
Median, IQR	1834 (1834–1834)	1834 (1834–1834)	
Total inpatient admissions			
Mean ± SD	46435±45217	75614±44808	<0.001[a]
Median, IQR	35194 (19315–61017)	67096 (39424–102059)	
Index treatment admission			
Mean ± SD	6959±2475	34052±22634	<0.001[a]
Median, IQR	7186 (4425–8607)	30143 (21209–41015)	
Rehabilitation after index treatment			
Mean ± SD	–	4901±380	N/A
Median, IQR		5140 (4322–5140)	
TOTAL COSTS			
Mean ± SD	80964±59182	110059±59671	0.005[a]
Median, IQR	66058 (43641–103229)	104374 (64125–144149)	

[†]$\chi 2$ test.
N, number; MWA, microwave ablation; CDC, Clavien-Dindo Classification; SD, standard deviation; IQR, interquartile range; MDT, multidisciplinary team; N, number; USD United States Dollars.
[a] Wilcoxon rank-sum test.
[b] Fisher's exact test.

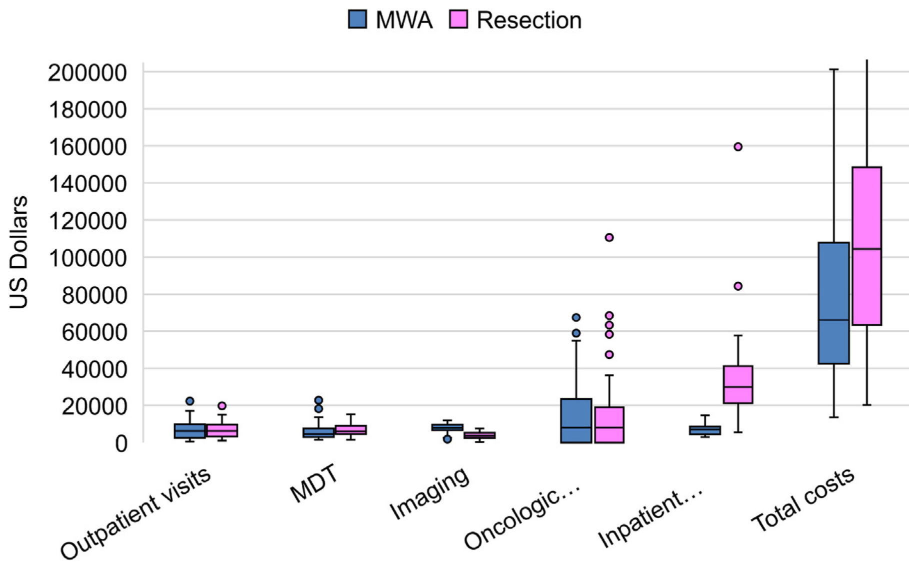

Fig. 2. Box plot of health care related costs from inclusion for index treatment at the liver multidisciplinary team conference (MDT) and two years onwards. In the Total costs category, one outlier in the microwave ablation (MWA) cohort located at USD 272′997 and the upper inter-quartile range (IQR) in the resection cohort at USD 248′478 are not shown.

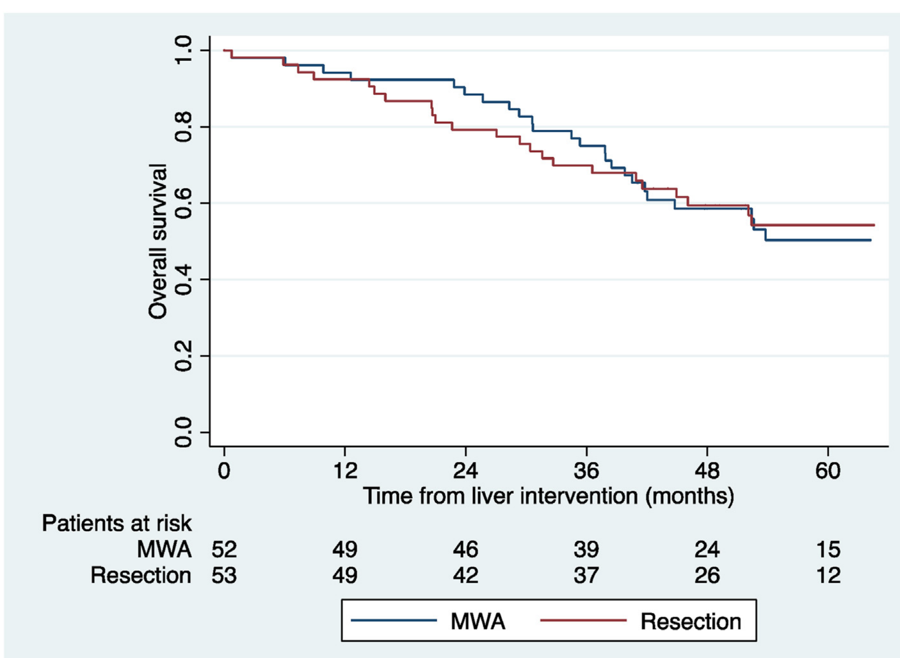

Fig. 3. Overall survival in the microwave ablation (MWA) versus resected patient cohorts. Log rank test P = 0.947, Wilcoxon test P = 0.831.

analyses. For liver specific recurrence rates, conflicting data exist when comparing thermal ablation to surgical resection for CRLM, with higher liver recurrence rates after ablation reported in systematic reviews [21]. In the current analysis, liver specific recurrence free survival was shorter in the MWA group, with more patients undergoing re-treatments for recurring CRLM within 2 years. These consisted mostly of repeat percutaneous thermal ablations, which has been shown to be a valid low-morbidity option for repeat treatment of recurring CRLM [22].

As the target population for curative-intended therapy becomes older with more severe comorbidity, the concept of repeat but low-morbidity treatments associated with short in-hospital stay is gaining importance [9]. Treatment related morbidity is well known to be decreased with thermal ablation compared to surgical resection for CRLM [21], which in turn is also relevant for patient survival [23]. Decreased morbidity, length of hospital stay and requirements for rehabilitation were confirmed in the current analysis, leading to decreased overall time spent in medical facilities. This underlines the hypothesis of reduced health care related costs and thus benefit the health care system when applying local thermal ablation as a first treatment choice for CRLM. Several studies investigated cost effectiveness, i.e. including quality-adjusted life years (QALY's), after thermal ablation versus surgical resection, based on estimation models using data extracted from previously

Table 3
Cox regression analysis on factors influencing overall survival in patients treated with resection or microwave ablation.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)[a]				
	1.029 (0.999, 1.061)	0.061	1.001 (0.959, 1046)	0.956
Sex				
Female (reference)	1	0.434		
Male	1.272 (0.696, 2.326)			
WHO performance status[a]				
0−1 (reference)	1	0.169	1	0.336
2−3	2.060 (0.735, 5.772)		1.683 (0.583, 4.860)	
Charlson comorbidity index[a]				
6−8 (reference)	1	0.036	1	0.333
≥ 9	1.906 (1.042, 3.486)		1.523 (0.583, 4.860)	
Primary tumour location				
Right (reference)	1	0.538		
Left	1.219 (0.661, 2.212)			
Primary tumour stage (pT)				
0−2 (reference)	1	0.045	1	0.065
3−4	2.858 (1.021, 7.994)		2.662 (0.942, 7.519)	
Primary tumour nodal stage (pN)				
0 (reference)	1	0.762		
1−2	1.105 (1.578, 2.114)			
Number of liver metastases				
1 (reference)	1	0.002	1	0.007
≥ 2	2.625 (1.434, 4.805)		2.432 (1.280, 4.623)	
Size of largest liver metastasis (millimeters)				
	1.015 (0.972, 1.060)	0.506		
Chemotherapy peri- liver intervention				
No (reference)	1	0.296		
Yes	1.358 (0.765, 2.411)			
Treatment approach				
MWA (reference)	1	0.947		
Resection	0.981 (0.553, 1.738)			

HR, Hazard Ratio; CI, Confidence Intervals; WHO, World Health Organization; MWA, microwave ablation.
[a] At time of liver intervention.

published studies, report conflicting results [7–9]. While earlier works favoured resection over ablation, and radiofrequency ablation (RFA) over MWA [7,9], the most recent study suggests enhanced cost-effectiveness with MWA over both RFA and surgical resection [8]. Another study based on clinical data comparing combined treatment strategies of thermal ablation and resection versus two-stage hepatectomy for bilobar CRLM favoured combined strategies including ablation in terms of cost effectiveness and survival [24]. In the current analysis based on prospectively collected clinical data in a quasi-randomised setting, reduced total health care related costs associated with MWA over resection were confirmed. This was mainly caused by reduced costs related to inpatient admissions, and significantly also due to the index treatment admission of MWA versus surgical resection. Despite using top-end computer-assisted navigation technology for percutaneous MWA treatment in a multidisciplinary team and a more expensive follow-up protocol. Hence, despite necessitating more repeat interventions related to liver specific recurrences, patients with CRLM treated with MWA spent less time in medical facilities including rehabilitation centres.

This reduced time spent as inpatients, a decreased treatment related morbidity and similarity in overall survival support the hypothesis that quality of life might be enhanced with minimally invasive thermal ablation as the initial intervention, especially in an older patient cohort [25–27]. Data on quality of life was not collected as part of the MAVERRIC study and hence not available for analysis in the current patient cohorts. No high quality prospectively collected data on quality of life after thermal ablation of CRLM are available to date, which is why we decided against the estimation of QALY's based on data from published literature and thus a formal cost-effectiveness analysis. The comparison of quality of life data from ongoing RCT's are desperately awaited and will yield important information on patient reported outcomes in the initial treatment of patients with CRLM [18,19]. In the meantime, it might be assumed that the initial treatment of CRLM likely does not influence quality of life significantly in the longer term, since patients suffer the same chronic colorectal cancer disease. This leads to similar oncology related health care consumption and disease-free survival as shown herein, and overall recurrences in around 70–75% of patients regardless of the initial type of treatment [2]. Hence, despite higher liver specific recurrences after MWA in the current analysis, shorter recurrence-free survival calculated after the first intervention probably reflects only marginally on the overall patient quality of life outcome [2].

The current study has several limitations. Even though the quasi-randomised setting led to two cohorts with similar baseline characteristics, a degree of inclusion bias certainly remained, e.g. due to inclusion of patients at the liver MDT conference and potential differences in the understanding of resectability and ablatability between different individuals. This element might exist even in true RCTs depending on inclusion criteria. While a discrepancy in the number of synchronous colorectal primary resection and liver treatments existed ($n = 16$ in the resection cohort, $n = 0$ in the MWA cohort), only one patient's complications were clearly related to the colorectal primary resection in the resection group. Also, complications rates have previously been shown to be similar with simultaneous liver and colorectal primary resections [28]. To allow combined treatments and reduce bias related to logistics, treatment options for entities like CRLM should optimally all be available in one facility. Lastly, due to the current analysis being a “spin-off" study from the MAVERRIC trial, the sample size was not predetermined for overall and recurrence free survival, potentially opening up for type 2 errors.

In conclusion, findings from this quasi-randomised trial suggest that treatment with MWA for patients with CRLM leads to similar long term overall survival rates as surgical resection, while being associated with significantly decreased morbidity, time spent in medical facilities and health care related costs within 2 years of treatment. Awaiting results from studies with prospectively collected data on quality of life, this supports the preferred initial use of thermal ablation as a minimally invasive treatment with curative intent, with regard to benefits to patients and health care systems.

CRediT authorship contribution statement

Pascale Tinguely: Formal analysis, Writing - original draft, Writing - review & editing. **Gustaf Laurell:** Formal analysis, Writing – review & editing. **Anton Enander:** Formal analysis, Writing – review & editing. **Jennie Engstrand:** Formal analysis, Writing – review & editing, Funding acquisition. **Jacob Freedman:** Conceptualization, Formal analysis, Writing – review & editing, Funding acquisition.

Declaration of competing interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Acknowledgement

The study was partially financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement. Jennie Engstrand was funded by Bengt Ihre Research Fellowship and supported by Region Stockholm (clinical postdoctoral appointment). Pascale Tinguely was funded by the Swiss Cancer League (BIL KLS-4894-08-2019). The funding sources had no involvement in the design or conduct of the study, the writing of the report or the decision to submit the article for publication.

References

[1] Mimmo A, Pegoraro F, Rhaiem R, Montalti R, Donadieu A, Tashkandi A, et al. Microwave ablation for colorectal liver metastases: a systematic review and pooled oncological analyses [Internet] Cancers 2022 Mar 3;14(5). Available from: http://www.ncbi.nlm.nih.gov/pubmed/35267612.

[2] Hof J, Wertenbroek MWJ, Peeters PMJG, Widder J, Sieders E, de Jong KP. Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases. Br J Surg 2016 Jul;103(8):1055–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27193207.

[3] Luo M, Chen S-L, Chen J, Yan H, Qiu Z, Chen G, et al. Resection vs. ablation for lesions characterized as resectable-ablative within the colorectal liver oligometastases criteria: a propensity score matching from retrospective study [Internet] PeerJ 2020;8:e8398. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32025372.

[4] Huang Z, Pan Y, Zhou P, Li S, Li K. Long-term outcomes of ultrasound-guided percutaneous microwave ablation versus resection for colorectal cancer liver metastases: a propensity-score matched study. Int J Hyperthermia 2021;38(1):1276–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34423716.

[5] Tinguely P, Dal G, Bottai M, Nilsson H, Freedman J, Engstrand J. Microwave ablation versus resection for colorectal cancer liver metastases - a propensity score analysis from a population-based nationwide registry. Eur J Surg Oncol 2020 Mar;46(3):476–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31837931.

[6] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol Off J Eur Soc Med Oncol 2016;27(8): 1386–422. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27380959.

[7] Gazelle GS, McMahon PM, Beinfeld MT, Halpern EF, Weinstein MC. Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection [Internet] Radiology 2004 Dec;233(3):729–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15564408.

[8] Froelich MF, Schnitzer ML, Rathmann N, Tollens F, Unterrainer M, Rennebaum S, et al. Cost-effectiveness analysis of local ablation and surgery for liver metastases of oligometastatic colorectal cancer [Internet] Cancers 2021 Mar 25;13(7). Available from: http://www.ncbi.nlm.nih.gov/pubmed/33806059.

[9] Loveman E, Jones J, Clegg AJ, Picot J, Colquitt JL, Mendes D, et al. The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. Health Technol Assess 2014 Jan;18(7). vii–viii, 1–283. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24484609.

[10] MAVERRIC trial. Available from: https://clinicaltrials.gov/ct2/show/NCT02642185?term=MAVERRIC&cntry=SE&rank=1.

[11] SweLiv (Internet), Last accessed 2022-06-13. Available from: https://cancercentrum.se/samverkan/cancerdiagnoser/lever-och-galla/kvalitetsregister/[Internet]. Available from: https://cancercentrum.se/samverkan/cancerdiagnoser/lever-och-galla/kvalitetsregister/.

[12] Engstrand J, Toporek G, Harbut P, Jonas E, Nilsson H, Freedman J. Stereotactic CT-guided percutaneous microwave ablation of liver tumors with the use of high-frequency jet ventilation: an accuracy and procedural safety study. AJR Am J Roentgenol 2017 Jan;208(1):193–200. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27762601.

[13] Tinguely P, Frehner L, Lachenmayer A, Banz V, Weber S, Candinas D, et al. Stereotactic image-guided microwave ablation for malignant liver tumors-A multivariable accuracy and efficacy analysis [Internet] Front Oncol 2020;10: 842. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32587826.

[14] Galmén K, Freedman J, Toporek G, Goździk W, Harbut P. Clinical application of high frequency jet ventilation in stereotactic liver ablations - a methodological study [Internet] F1000Research 2018;7:773. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30271582.

[15] Engstrand J, Strömberg C, Nilsson H, Freedman J, Jonas E. Synchronous and metachronous liver metastases in patients with colorectal cancer-towards a clinically relevant definition [Internet] World J Surg Oncol 2019 Dec 26;17(1): 228. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31878952.

[16] Dindo D, Demartines 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 Aug;240(2):205–13. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-200408000-00003.

[17] Gurusamy K, Corrigan N, Croft J, Twiddy M, Morris S, Woodward N, et al. Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases (LAVA): study protocol for a randomised controlled trial [Internet] Trials 2018 Feb 13;19(1):105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29439711.

[18] Puijk RS, Ruarus AH, Vroomen LGPH, van Tilborg AAJM, Scheffer HJ, Nielsen K, et al. Colorectal liver metastases: surgery versus thermal ablation (COLLISION) - a phase III single-blind prospective randomized controlled trial. BMC Cancer 2018 Aug 15;18(1):821. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30111304.

[19] NEW-COMET trial. Available from: https://clinicaltrials.gov/ct2/show/NCT05129787?term=new-comet&draw=2&rank=1.

[20] Di Martino M, Rompianesi G, Mora-Guzmán I, Martín-Pérez E, Montalti R, Troisi RI. Systematic review and meta-analysis of local ablative therapies for resectable colorectal liver metastases. Eur J Surg Oncol 2020;46(5):772–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31862133.

[21] Meijerink MR, Puijk RS, van Tilborg AAJM, Henningsen KH, Fernandez LG, Neyt M, et al. Radiofrequency and microwave ablation compared to systemic chemotherapy and to partial hepatectomy in the treatment of colorectal liver metastases: a systematic review and meta-analysis [Internet] Cardiovasc Intervent Radiol 2018 Aug;41(8):1189–204. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29666906.

[22] Dijkstra M, Nieuwenhuizen S, Puijk RS, Timmer FEF, Geboers B, Schouten EAC, et al. Thermal ablation compared to partial hepatectomy for recurrent colorectal liver metastases: an amsterdam colorectal liver met registry (AmCORE) based study [Internet] Cancers 2021 Jun 2;13(11). Available from: http://www.ncbi.nlm.nih.gov/pubmed/34199556.

[23] Dorcaratto D, Mazzinari G, Fernandez M, Muñoz E, Garcés-Albir M, Ortega J, et al. Impact of postoperative complications on survival and recurrence after resection of colorectal liver metastases: systematic review and meta-analysis. Ann Surg 2019;270(6):1018–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30829704.

[24] Abbott DE, Sohn VY, Hanseman D, Curley SA. Cost-effectiveness of simultaneous resection and RFA versus 2-stage hepatectomy for bilobar colorectal

liver metastases. J Surg Oncol 2014 May;109(6):516–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24374772.

[25] Yang S, Alibhai SMH, Kennedy ED, El-Sedfy A, Dixon M, Coburn N, et al. Optimal management of colorectal liver metastases in older patients: a decision analysis (Oxford) [Internet] HPB 2014 Nov;16(11):1031–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24961482.

[26] Ruers TJM, Joosten JJ, Wiering B, Langenhoff BS, Dekker HM, Wobbes T, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. Ann Surg Oncol 2007 Mar;14(3):1161–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17195903.

[27] Khajanchee YS, Hammill CW, Cassera MA, Wolf RF, Hansen PD. Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: a Markov analysis. Arch Surg 2011 Dec;146(12):1416–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22288086.

[28] Boudjema K, Locher C, Sabbagh C, Ortega-Deballon P, Heyd B, Bachellier P, et al. Simultaneous versus delayed resection for initially resectable synchronous colorectal cancer liver metastases. Ann Surg 2021 Jan;273(1):49–56. Available from: https://journals.lww.com/10.1097/SLA.0000000000003848.