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Original Research

A prospective multicentre trial on survival after Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases (MAVERRIC)

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Abstract ***Aim:*** This multi-centre prospective cohort study aimed to investigate non-inferiority in patients' overall survival when treating potentially resectable colorectal cancer liver metastasis (CRLM) with stereotactic microwave ablation (SMWA) as opposed to hepatic resection (HR).
Methods: Patients with no more than 5 CRLM no larger than 30 mm, deemed eligible for both SMWA *and* hepatic resection at the local multidisciplinary team meetings, were deliberately treated with SMWA (study group). The contemporary control group consisted of patients with no more than 5 CRLM, none larger than 30 mm, treated with HR, extracted from a prospectively maintained nationwide Swedish database. After propensity-score matching, 3-year overall survival (OS) was compared as the primary outcome using Kaplan-Meier and Cox regression analyses.

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Results: All patients in the study group (n = 98) were matched to 158 patients from the control group (mean standardised difference in baseline covariates = 0.077). OS rates at 3 years were 78% (Confidence interval [CI] 68–85%) after SMWA versus 76% (CI 69–82%) after HR (stratified Log-rank test $p = 0.861$). Estimated 5-year OS rates were 56% (CI 45–66%) versus 58% (CI 50–66%). The adjusted hazard ratio for treatment type was 1.020 (CI 0.689–1.510). Overall and major complications were lower after SMWA (percentage decrease 67% and 80%, $p < 0.01$). Hepatic retreatments were more frequent after SMWA (percentage increase 78%, $p < 0.01$).

Conclusion: SMWA is a valid curative-intent treatment alternative to surgical resection for small resectable CRLM. It represents an attractive option in terms of treatment-related morbidity with potentially wider options regarding hepatic retreatments over the future course of disease.

1. Introduction

Colorectal cancer is the second most common cause of cancer-related death worldwide, with 1.9 million new cases and almost 1.0 million deaths annually in 2020 [1]. Approximately 30% of patients with colorectal cancer develop colorectal cancer liver metastasis (CRLM) during the course of disease [2]. Hepatic resection (HR) has been the gold standard for treatment of CRLM with curative intent, with reported median 5-year survival of around 40% [3]. Over the last decades, thermal ablation such as radiofrequency ablation (RFA) and microwave ablation (MWA) has been established as treatment alternatives to HR, mainly for small CRLM smaller than 3 cm, as adjunct to HR or as completion treatment [4,5]. Thermal ablation was included in current treatment guidelines as an alternative to HR for selected patients with oligometastatic disease [6,7]. The main benefits of thermal ablation include its tissue-sparing nature, targeting tumours with maximal sparing of surrounding liver tissue, and its easy application as a minimally invasive percutaneous approach. Treatment efficacy can further be enhanced by using stereotactic navigation technology for precise targeting of liver tumours and validation of treatment success [8,9]. These characteristics significantly reduce treatment-related morbidity, hospitalisation time and associated health-related costs, and to enhance options for retreatments in case of CRLM recurrence [10–12]. Regarding oncological outcomes, several non-randomised observational studies show similar recurrence-free and overall survival (OS) after thermal ablation compared to HR [13–16]. However, results from high-quality prospective studies or randomised controlled trials (RCT) regarding survival outcomes are lacking, and reluctance with regard to a broader application of thermal ablation persist.

The aim of this prospective cohort study was to investigate the hypothesis of non-inferiority in OS after stereotactic microwave ablation (SMWA) versus HR for potentially resectable small CRLM.

2. Material and methods

2.1. Study design and study population

This prospective multicentre cohort study was performed in three European tertiary Hepato-Pancreato-Biliary Surgery centres (Inselspital, University Hospital of Bern, Bern, Switzerland; University Medical Center Groningen, Groningen, Netherlands; and Danderyd Hospital/Karolinska Institute, Stockholm, Sweden) and registered at clinicaltrials.gov (NCT02642185). The study protocol was approved by all three respective regional ethical review boards (Bern: Kantonale Gesundheitskommission (KEK) Bern 317/15, Groningen: 2016/004, Stockholm: Dnr 2015/1453-31/4).

Patients with CRLM were eligible for study inclusion when fulfilling the following criteria: i) one to five liver tumours no larger than 30 mm in diameter, and ii) considered eligible for both HR *and* computed tomography (CT)-guided SMWA with curative intention, as decided at the locoregional multi-disciplinary tumour board (MDT) meetings. Exclusion criteria for HR or SMWA were applied as per the current treatment standards, including the preservation of sufficient well-perfused hepatic parenchyma with adequate drainage (HR) and avoiding the risk of causing thermal damage to hollow viscus or central bile structures (SMWA). Further exclusion criteria were i) previous thermal ablation of CRLM, ii) more than two previous liver resections for CRLM, iii) previous hyperthermic intraperitoneal chemotherapy (HIPEC) treatment for colorectal cancer, iv) non-pulmonary extrahepatic colorectal cancer metastases, and v) patients with renal failure limiting the use of intravenous contrast agents for SMWA.

Patients who were eligible for both HR *and* SMWA and accepted inclusion in the present study were deliberately treated by SMWA (study cohort). Written informed consent for study inclusion and treatment with SMWA was obtained from every patient. Study

inclusion time was between December 2015 and December 2018. In Bern and Groningen all patients meeting the inclusion criteria were offered study participation, whereas in Stockholm patients were considered for study inclusion only every other week, to avoid delays in SMWA treatment, which is centralised to one hospital in the greater Stockholm area. CT-guided stereotactic guidance was chosen for tumour targeting and positioning of the ablation antenna, as it represents the highest-standard, reproducible precision treatment for thermal ablation of liver tumours, allowing standardised planning of ablation antennae trajectories, quantitative documentation of targeting precision and immediate treatment evaluation by direct overlay of pre- and post-ablation images [9]. Microwave energy was chosen as ablation technology due to its more effective treatment profile as compared to RFA for treatment of CRLM [17,18].

The control cohort consisted of patients with CRLM with the same selection criteria (maximum number of 5 CRLM with a maximum diameter of 30 mm at the MDT meeting), treated with HR between March 2015 to December 2018, extracted from the Swedish Liver Registry (SweLiv) [19]. The SweLiv registry is a prospectively maintained, population-based nationwide Swedish registry containing data on surgical and interventional treatments of liver tumours in all patients older than 16 years. The coverage rate of the SweLiv registry was described to cover 96% of all patients diagnosed with CRLM in Sweden as compared with the Swedish Cancer Registry. Data from SweLiv was complemented with clinical data from the Swedish colorectal cancer registry (SCRCR) [20] regarding clinical factors of the primary colorectal tumour and from the National Patient Register (NPR) [21] regarding patient comorbidities. The shift in inclusion time corresponded to the difference in follow-up time between the study group (date of latest follow-up 10th August 2022) and the control group (date of data extraction 19th October 2021).

Primary study endpoint was OS after 3 years. Secondary endpoints included analyses on local tumour progression (LTP) [22], on treatment-related costs [11] and of long-term OS at 5 and 10 years. Further secondary endpoints included detailed volumetric analyses on the dimensions of created ablation volumes and on ablation margins in the SMWA cohort [23,24].

2.2. SMWA procedure and follow-up

SMWA procedures were performed in interventional CT suites by an interdisciplinary team consisting of specifically trained interventional radiologists and hepatobiliary surgeons with large experience in image-guided tumour ablation (all operators have performed > 100 SMWA procedures). Patients were treated under general anaesthesia using High-Frequency Jet ventilation [25] or controlled apnoea during image acquisition and ablation antennae positioning. Ablation antenna trajectory planning, stereotactic antenna positioning and verification of treatment success were performed using the CAS-ONE system (Cascination AG, Bern, Switzerland) or the Needle Positioning System (NPS; DEMCON Advanced Mechatronics, Enschede, the Netherlands). Respective workflows have previously been described in detail [26–28]. Single-antenna MWA was performed with the Acculis (Angiodynamics, Latham, NY USA), Amica (HS Hospital service S.P.A, Roma, Italy) or Emprint (Covidien, Minneapolis, USA) system. A contrast-enhanced CT scan including a portal venous phase was performed immediately after ablation antenna extraction for validation of technical success by visual overlay of co-registered pre- and post-ablation images. Technical success was defined as complete coverage of the tumour by the ablation zone plus an ablation margin of ideally 5–10 mm. If this was not achieved, immediate re-ablation was performed.

The first follow-up cross-sectional imaging (magnetic resonance imaging or CT) was performed within 3 months after the SMWA procedure, followed by imaging every 3–4 months during the first year and every 4–6 months thereafter, applying standardised terminology and reporting criteria [29]. LTP was defined as the appearance of tumour foci at the edge of the ablation zone within 1 year after SMWA [30]. With regards to OS, the minimum follow-up period of surviving patients was 36 months after the index treatment.

2.3. Data extraction and definitions

Patient and tumour characteristics, treatment-related and follow-up data were extracted from the prospective study database. Data from the control cohort were received from the respective nationwide registries. Patient comorbidities were classified according to the Charlson comorbidity index (CCI) [31]. Clinical complications were registered according to the Clavien-Dindo classification [32].

2.4. Statistical analyses

A sample size calculation was performed by applying computer-simulated random sampling. OS curves from 1387 patients after HR of a single CRLM tumour smaller than 30 mm (best case scenario) were extracted from the LiverMetSurvey dataset [33] using the Kaplan-Meier method. The survival probabilities of a random sample of 100 patients were compared at a non-inferiority level of 10% below the lower 90% confidence interval at 3 years after surgery (power of 90%), yielding a number of 92 patients to be included in the study cohort. To allow for potential dropouts, a sample size of 100 patients was decided.

A propensity score analysis, as opposed to regression modelling, was chosen to address the effect of

confounding, since it allows an estimation of marginal effects at the population level, an easier verification of adequate model specification, more transparent analysis of the overlap in the distribution of baseline covariates across cohorts and a separation of model design and outcome analysis similar to RCT's [34]. A propensity score-matched analysis was performed following the 'conduct and reporting of propensity score methods on time-to-event outcomes using observational data', proposed by Peter C. Austin [35]. First, a propensity score model was fitted using a logistic model regressing treatment status on the baseline covariates listed in Table 1. Adequate specification of the model was confirmed by investigating the balance of the propensity score across treatment groups, and of covariates within blocks of the propensity score across groups [36]. Second, a many-to-one nearest neighbour matching was performed, allowing a maximum number of two controls to minimise the mean squared error [34,37]. A caliper width of 0.2 of the standard deviation of the logit of the propensity score was applied [38]. Matching with replacement, imposing a common support and allowing for ties were specified. Balance of covariates across treatment groups after matching was assessed by calculating weighted (accounting for the many-to-one setting [39]) standardised differences, with a threshold of 0.1 considered as indication of adequate balance across cohorts [40]. To avoid new selection bias introduced by the propensity score matching itself, survival outcomes were compared between matched patients and non-matched patients in the HR cohort. Alternative propensity-score matching techniques were applied to compare results when trading the adequacy of matching and thus reduction of bias, with an improvement of statistical power and thus generalisability by including more patients from the control group.

Survival was calculated as the time from index treatment (SMWA in the study cohort or the date of HR in the control cohort) to the time of death from any diagnosis or censored at the date of last follow-up. Actual absolute treatment effects were calculated in the matched cohorts as OS proportions and 95% confidence intervals (CI) at 3 years after index treatment, and OS estimated at 5 years, using the Kaplan-Meier method. A stratified (accounting for lacking independency of observations in matched samples [35]) Log-rank test was applied to compare survival curves in the matched cohorts. Relative treatment effect on the hazard of death was estimated using Cox proportional hazard models, regressing survival on the treatment status, with a robust variance estimator to account for potential clustering within matched cohorts [35]. The assumption of proportional hazards was confirmed by testing Schoenfeld residuals and the non-significance of adding a time-dependent interaction term to the model. The threshold for statistical significance was set to $\alpha < 0.05$. STATA/IC version 16.0 (StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA) was used for statistical analyses. The code and output of statistical analyses are available as Supplementary Results.

3. Results

One hundred and eight patients were enrolled between December 2015 and December 2018. One patient was excluded after a biopsy performed immediately prior to SMWA unexpectedly revealed a liver metastasis from prostate cancer rather than from colorectal cancer. Nine patients were excluded due to screening failure, including three due to previous liver ablation treatment, four due to previous HIPEC treatment and two due to ablation with radiofrequency (RFA) instead of SMWA. This resulted in a study cohort of 98 patients with a total of 168 CRLM treated with SMWA. The control cohort consisted of 692 subjects eligible for propensity score matching (Fig. 1).

The fitted propensity score model yielded full overlap in the range of propensity scores (= full "common support") with a similar distribution ('balance') across cohorts (Supplementary Results). Propensity score matching yielded a total study cohort of n = 256, with 100% of patients from the study cohort (n = 98) matched to 158 subjects from the control cohort. Baseline patient and tumour characteristics before and after matching are shown in Table 1. Two balanced groups were obtained with respect to i) the balancing property of the propensity score distribution across cohorts (Supplementary Results), and ii) the distribution of baseline covariates, with a mean standardised difference in all covariates across treatment groups dropping from 0.191 before matching to 0.077 after matching. A comparison of sample sizes, mean standardised differences across treatment groups and absolute and relative average treatment effects, in the original sample and when applying different matching strategies, is shown in Table 2.

In the matched cohorts, the median (IQR) number of treated CRLM was 1 (1, 2) in the SMWA group and 1 (1, 2) in the HR group. The median (IQR) tumour size was 16 mm (12 mm, 23 mm) in the SMWA cohort, and 18.5 mm (15 mm, 25 mm) in the matched HR cohort. One (1%) patient in the SMWA cohort had concomitant lung metastasis, which was resected within 5 months after SMWA, versus nine in the matched HR cohort (6%).

Median follow-up time was 51 (Interquartile range IQR 38–61) months in the SMWA cohort and 47 (IQR 36–64) months in the HR cohort. The actual 3-year OS rates at 3 years after SMWA versus HR were 78% (CI 68–85%) versus 76% (CI 69–82%). Estimated 5-year OS rates were 56% (CI 45–66%) versus 58% (CI 50–66%), respectively (stratified Log-rank test $p = 0.861$) (Fig. 2). Cox regression analysis yielded a relative change in the hazard of death (Hazard ratio, HR) of 1.020 (CI 0.689–1.510) ($p = 0.921$) induced by the treatment type.

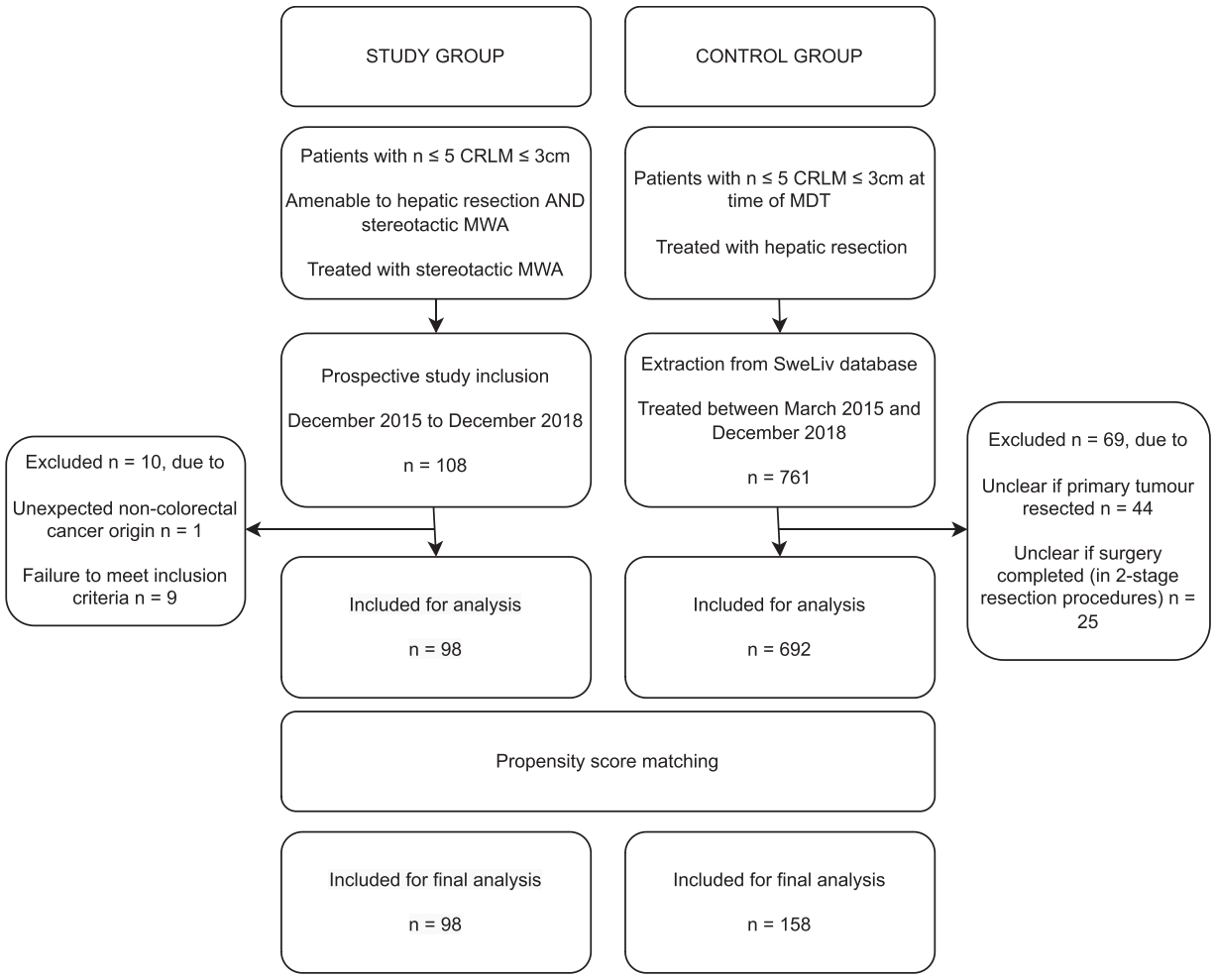

Fig. 1. Flowchart of study inclusion and design. CRLM, colorectal cancer liver metastases; MWA, microwave ablation; MDT, multidisciplinary team meeting.

Multivariable analysis yielded the ASA and CCI category, the primary tumour T stage and the size of the largest CRLM as the covariates to statistically significantly influence OS in the matched cohorts (Fig. 3).

When comparing the matched patients from the control group (HR) versus the non-matched patients from the control group (HR), the estimated probability of 3-year OS was 76% (CI 69–82%) in the matched versus 70% (CI 66–73%) in the non-matched patients (Log-rank test $p = 0.346$) (Supplementary Results).

Of the 168 CRLM treated with SMWA in the study group, 3 (1.8%) were located in liver segment I, 7 (4.2%) in segment II, 13 (7.7%) in segment III, 16 (9.5%) in segment IV, 13 (7.7%) in segment V, 22 (13.1%) in segment VI, 52 (31%) in segment VII and 42 (25%) in segment VIII. Eighty-two (48.8%) tumours were located in subcapsular positions (≤5 mm from liver capsule). Technical success rate was 96% (seven tumours incompletely ablated at first radiological follow-up). Six tumours underwent completion ablation within 1 month, leading to a primary efficacy rate of 99%. The LTP rate within 1 year of follow-up was 17% (28 of 168 CRLM). Of the 28 tumours with LTP, 14 were successfully re-treated with SMWA, leading to a secondary efficacy rate of 92%. Sixteen (70%) of 23 patients with LTP had concomitant new intrahepatic tumours, and four (17%) had concomitant extrahepatic disease.

Of the 158 matched patients that underwent HR in the control group, 22 (14%) had major resections (trisectionectomies, hemihepatectomies), 135 (85%) resections of one to three segments, atypical or wedge resections, and one other resections. Twenty-nine (18%) HR were performed via laparoscopic treatment access, the rest via an open approach. In the HR cohort, 48 (30%) had a complication within 30 d of follow-up versus 10 (10%) in the SMWA cohort (percentage decrease 67%). Of these, 16 (10%) versus 2 (2%) were major complications (Clavien-Dindo grade 3a to 5) (percentage decrease 80%), and 32 (20%) versus 8 (8%) were minor complications (Clavien-Dindo grade 1–2) ($p < 0.01$ Fisher's exact test). The two major complications in the SMWA cohort were one patient requiring pleural drainage after a haemothorax, and one patient who died from a cardiac event after surgical re-

Table 1
Baseline patient and tumour characteristics before and after matching

	Crude data (n = 790)				*Propensity score-matched data (n = 256)*			
	MWA (n = 98)	**Resection (n = 692)**	***p-value***	***D*[a]**	**MWA (n = 98)**	**Resection (n = 158)**	***p-value***	***D*[a]**
Age (years)[b]								
Overall[c]	68 (62, 74)	68 (61, 73)	0.796[d]	−0.083	68 (62, 74)	68 (61, 74)	0.761[d]	−0.099
≤55	11 (11)	90 (13)	0.599	0.145	11 (11)	24 (15)	0.710[f]	0.152
56–65	27 (28)	186 (27)			27 (28)	44 (28)		
66–75	38 (39)	297 (43)			38 (38)	62 (39)		
> 75	22 (23)	119 (17)			22 (23)	28 (18)		
Sex ratio								
Male: Female	65 (66): 33 (34)	423 (61): 270 (39)	0.322[e]	−0.108	65 (66): 33 (34)	104 (66): 54 (35)	0.934[e]	−0.011
American Society of Anesthesiologists (ASA) score								
1–2	59 (60)	516 (75)	0.002[e]	−0.324	59 (60)	101 (64)	0.550[e]	−0.076
3–4	39 (40)	170 (25)			39 (40)	57 (36)		
Unknown		6						
Charlson comorbidity index[b]								
6 / 7	15 (15)	171 (25)	< 0.001[f]	0.482	15 (15)	22 (14)	0.309[f]	0.191
8 / 9 / 10	71 (73)	492 (72)			71 (73)	125 (80)		
≥11	12 (12)	19 (3)			12 (12)	11 (7)		
Unknown		10						
Primary tumour location								
Right-sided	29 (30)	167 (24)	0.242[e]	0.123	17 (17)	24 (15)	0.647[e]	0.067
Left-sided	69 (70)	525 (76)			81 (83)	134 (85)		
Primary tumour stage (pT)								
0–2	17 (17)	97 (14)	0.410[e]	0.086	17 (17)	27 (18)		
3–4	81 (83)	586 (86)			81 (83)	124 (82)	0.914[e]	0.058
Unknown		9						
Primary tumour nodal stage (pN)								
0	38 (39)	224 (33)	0.241[e]	0.126	38 (39)	66 (42)		
1–2	60 (61)	459 (67)			60 (61)	92 (58)	0.635[e]	−0.061
Unknown		9						
No. of liver metastases[b]								
1	54 (55)	340 (49)	0.552[f]	0.118	54 (55)	94 (60)	0.680[f]	0.114
2–3	35 (36)	282 (41)			35 (36)	48 (31)		
4–5	9 (9)	68 (10)			9 (9)	16 (10)		
Unknown		2						
Size of largest liver metastasis[b]								
< 11	17 (17)	153 (22)	0.495[f]	0.136	17 (17)	29 (18)	0.985[f]	0.029
11–20	47 (48)	294 (43)			47 (48)	74 (47)		
> 20	34 (35)	245 (35)			34 (35)	55 (35)		
First liver intervention[b]								
No	16 (16)	65 (9)	0.034[e]	0.208	16 (16)	26 (16)	0.978[e]	-0.004
Yes	82 (84)	627 (91)			82 (84)	132 (84)		
Neoadjuvant chemotherapy[b]								
No	66 (67)	361 (52)	0.005[e]	0.312	66 (67)	100 (63)	0.509[e]	0.085
Yes	32 (33)	331 (48)			32 (33)	58 (37)		

[a] Standardised mean difference.
[b] At time of liver intervention.
[c] Values in median (IQR).
[d] Wilcoxon rank-sum test.
[e] $\chi 2$ test.
[f] Fisher's exact.

intervention due to a liver abscess with gastrointestinal fistula. There were no mortalities in the matched HR group. Within the 3-year follow-up period, 47 (48%) of the 98 patients in the SMWA group underwent a total of one to seven retreatments for hepatic CRLM recurrences, while 42 (27%) of the 158 patients in the matched HR group underwent one to four hepatic retreatments (percentage increase 78%, $p < 0.01$ Fisher's exact test). This included retreatments for LTP and for new intrahepatic CRLM. In the SWMA group, 77 (85%) of 91 repeat interventions were thermal ablations and 14 (15%) were surgical resections. In the HR group, 29 (59%) of 49 repeat interventions were thermal ablations and 20 (41%) were surgical resections.

Table 2
Comparison of sample size, balance across all baseline covariates and absolute and relative treatment effects in original sample and with different matching strategies

Sample type	Total sample size	Number of observations in study cohort	Number of observations in control cohort	(Weighted[a]) Mean standardised differences across all covariates between study and control cohorts	Mean absolute difference in 3-year overall survival probability (SMWA versus resection) (%)	(Stratified[a]) Log-rank test comparing overall survival curves (*p*-value)	Mean relative change in the hazard of death in univariable model (Hazard ratio)	Bias due to potential loss of statistical power	Bias due to potential residual confounding
Original sample before matching	790	98	692	0.191	6.5	0.631	0.923		
Caliper 0.2 1:5 controls Allowing ties	404	98	306	0.084	5.3	0.421	0.923		
Caliper 0.21:2 controlsAllo-wing ties	**256**	**98**	**158**	**0.077**	**2.0**	**0.861**	**1.020**		
Caliper 0.2 1:2 controls Not allowing ties	249	98	151	0.081	1.4	0.952	1.038		
Caliper 0.2 1:1 controls Allowing ties	200	98	102	0.088	3.0	0.468	0.928		

SMWA, Stereotactic microwave ablation.
[a] In matched sample types.

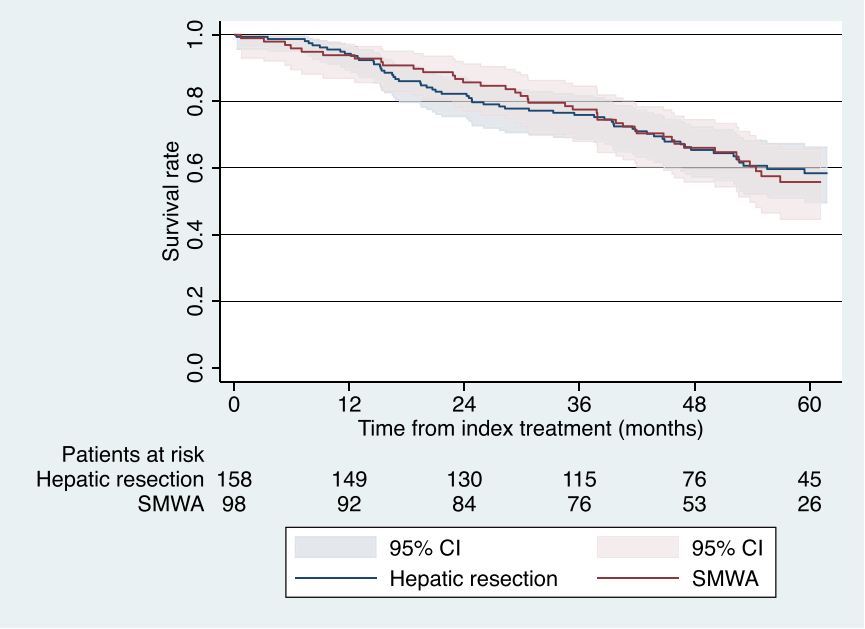

Fig. 2. Overall survival of patients after stereotactic microwave ablation (red) and hepatic resection (blue). Stratified Log-rank $p = 0.861$. SMWA, stereotactic microwave ablation; CI, confidence interval.

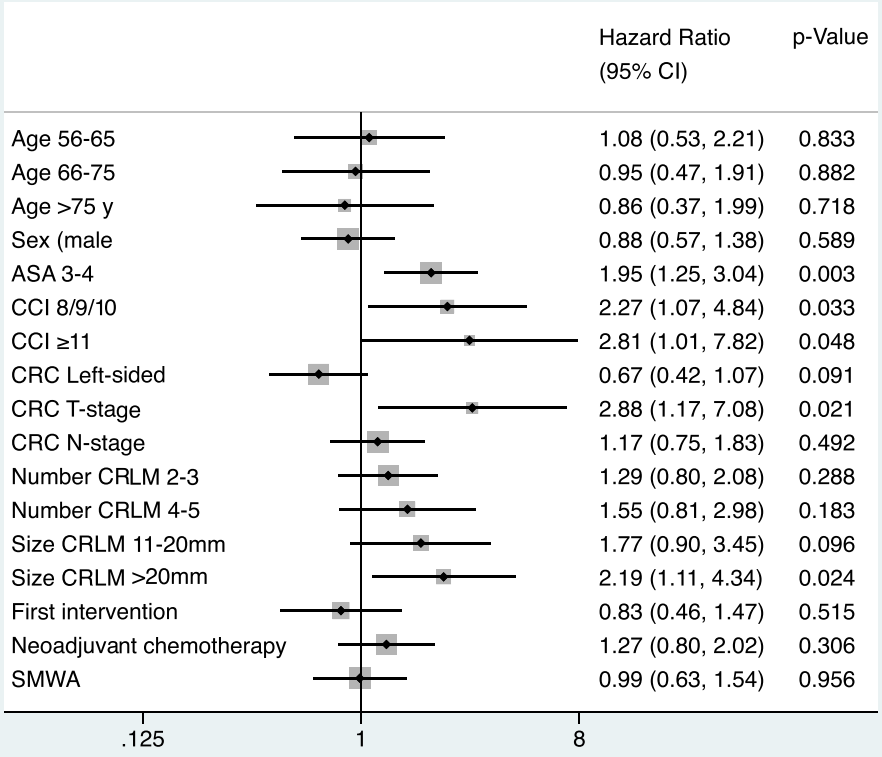

Fig. 3. Multivariable analysis on the effect of covariates on overall survival after index treatment. The reference categories for each covariate (not shown) correspond to the respective first row in Table 1. ASA, American Society of Anesthesiologists; CCI, Charlson comorbidity index; CRC, colorectal cancer; CRLM, colorectal cancer liver metastasis; SMWA, stereotactic microwave ablation.

4. Discussion

Results from this prospective cohort trial show that treatment of small, resectable CRLM with SMWA results in similar patient OS as observed after HR, with significantly less treatment-associated morbidity. To the best of our knowledge, this is the first prospective cohort trial comparing thermal ablation for resectable CRLM with outcomes after HR.

Thermal ablation remains controversial as an initial treatment of patients with potentially resectable CRLM, with conflicting results reported in systematic literature reviews [41,42]. Importantly, no RCT or well-designed prospective studies have been published comparing oncological endpoints of thermal ablation for potentially resectable CRLM. Ongoing RCTs are delayed or failed in patient inclusion [43,44]. Reasons are multi-factorial and include the complexity of clinical trial design when aiming to show non-inferiority in oncological end-points with adequate statistical power. Furthermore, unbiased 'clinical equipoise' is difficult to reach when including patients for treatments performed by clinicians with varying background (e.g. HR by surgeons versus thermal ablation by interventional radiologists) [43]. While awaiting results from the currently ongoing RCTs (COLLISION trial NCT03088150, NEW-COMET trial NCT05129787 and HELARC trial NCT02886104), the current clinical trial was designed as a prospective cohort study, deliberately including patients with potentially resectable CRLM for SMWA treatment based on informed consent. This yielded survival curves after SMWA which are not affected by inclusion bias, as are most estimations and comparisons from retrospective series [45]. While the possibility of thermal ablation as an alternative to HR in patients from the control group was unknown, this was partially addressed by accounting for number and size of CRLM when creating the propensity score. Further strengths of the current study design include the choice of a validated, population-based, nationwide database as the control group. Despite seeking maximal bias reduction using conservative estimators for propensity score-matching, this yielded an inclusion of 100% of study patients and an adequate matched sample as a control group. The similarity of OS rates in the matched and non-matched patients from the control group reduces a potential concern that patients with inferior OS were selected for matching. The main result of similar 3-year OS rates after SMWA and HR for patients with resectable CRLM is therefore encouraging. The fact that varying matching strategies led to similar outcomes (Table 2), even when including up to five controls or when applying a strict 1-to-1 matching, further strengthens the validity of obtained results. The obtained OS rates of 77% in both groups correspond to previously published OS probabilities [13–16].

The well-known significantly lower treatment-associated morbidity with thermal ablation compared to HR was confirmed in this study [41]. Using a percutaneous treatment access for SMWA and applying the highest available technological standards for stereotactic tumour targeting probably contributed to further reducing complication rates [9]. A recently published consensus-based guideline on resectability and ablatability criteria for patients with curative-intent treatment of CRLM suggests a central tumour location to be a valid criterion for thermal ablation [7]. When targeting such central intrahepatic tumours, avoiding harm to central vascular and biliary structures, and thus stereotactic precision in the positioning of ablation antennae, is crucial [46]. Using sophisticated navigation technology allows to effectively target malignant liver tumours located in traditionally difficult-to-target intrahepatic locations [9]. This allowed for effective SMWA treatment of CRLM located in all liver segments in the current study (99% primary efficacy). The evaluation of technical success evaluation might be further enhanced by adding novel radiomics and algorithms for 3D ablation margin assessment into the routine SMWA workflow, which was not yet the case during this study [22,49,50]. This will also allow a more accurate differentiation of technical success from true LTP, and analyses of factors influencing their incidence. The LTP rate of 17% was at the higher end of previously reported per-tumour analyses [47,48], which was probably influenced by the 70% concomitant new intrahepatic tumours, indicating more aggressive tumour biology in these patients.

In the current trial, no data on hepatic or distant colorectal cancer recurrences were available from the control group; however, hepatic retreatments were more frequent in the SMWA versus the HR cohort. Overall, results suggest that neither the type of initial treatment nor the number or type of retreatments significantly affect the OS of patients with CRLM. This parallels results from previous studies showing that recurrence-free survival and the radicality of the initial treatment do not affect OS [51–53]. Considering the high recurrence rate of colorectal cancer of 70% after initial treatment of CRLM, leading to retreatments in around 50% of recurrent cases [10], opting for the safest, most tissue-sparing and cost-effective initial treatment optimises the choice for future repeat treatments [54]. Reducing the loss of healthy liver parenchyma further increases hepatic tolerance to interval chemotherapy [55]. Results on associated quality of life after CRLM treatment and on patient resilience towards repeat invasive treatments over the course of disease are currently missing and eagerly awaited [44]. With advancements in colorectal cancer screening programs and in radiological technology, detection of a larger portion of small CRLM at an earlier stage can be expected, leaving patients with potentially longer courses of disease ahead. This will further enhance the attractiveness of applying tissue-sparing, low-morbidity treatments that allow the most options for future

retreatments. A change in treatment policies towards the safest and most sustainable curative-intent treatment options over the course of the disease will be inevitable.

One limitation of the study is the remaining confounding arising due to its observational study design. We minimised this by performing a meticulous verification of the propensity-score technique allowing the reduction of remaining bias and the creation of two comparable cohorts conditional on the propensity score [34]. Another limitation is the use of registry-based data as the control cohort, restricting data availability in this group to what was previously collected as part of the nationwide database. This included data on tumour recurrence, on potential ablatability of CRLM in patients from the control group, on factors known to affect survival in resectable CRLM (such as carcinoembryonic antigen (CEA) levels, KRAS mutation of the colorectal primary or microsatellite instability) and details on chemotherapy regimen [56,57]. These covariates could not be included in the design of the propensity score. Nevertheless, factors identified to affect survival in the matched cohort such as CRLM size and patient comorbidity were similar as in previous studies [3,58].

In conclusion, results from this prospective multicentre trial support the role of SMWA as a valid curative-intent treatment alternative for patients with small CRLM. This supports a probable shift towards more interventional, minimally invasive and tissue-sparing treatments, and might aid decision-making when designing treatment policies and defining personalised therapeutic algorithms for patients with metastatic colorectal cancer disease.

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CRediT authorship contribution statement

Pascale Tinguely: Conceptualisation; Data curation; Formal analysis; Methodology; Writing – original draft; **Simeon J.S. Ruiter:** Data curation; Formal analysis; Methodology; Writing – original draft; **Jennie Engstrand:** Conceptualisation; Data curation; Methodology; Validation; Writing – review & editing. **Robbert J. de Haas:** Supervision; Validation; Writing – review & editing. **Henrik Nilsson:** Conceptualisation; Data curation; Methodology; Validation; Writing – review & editing. **Daniel Candinas:** Conceptualisation; Methodology; Resources; Supervision; Writing – review & editing. **Koert P. de Jong:** Conceptualisation; Data curation; Methodology; Resources; Supervision; Writing – review & editing. **Jacob Freedman:** Conceptualisation; Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Supervision; Validation; Writing – review & editing.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.03.038.

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