Thermal ablation versus surgical resection of small-size colorectal liver metastases (COLLISION): an international, randomised, controlled, phase 3 non-inferiority trial

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Summary

Background For patients with small-size colorectal liver metastases, growing evidence suggests thermal ablation to be associated with fewer adverse events and faster recovery than resection while also challenging resection in terms of local control and overall survival. This study assessed the potential non-inferiority of thermal ablation compared with surgical resection in patients with small-size resectable colorectal liver metastases.

Methods Adult patients (aged ≥18 years) from 14 centres in the Netherlands, Belgium, and Italy with ten or fewer small-size (≤3 cm) colorectal liver metastases, no extrahepatic metastases, and an Eastern Cooperative Oncology Group performance status of 0–2, were stratified per centre, and according to their disease burden, into low, intermediate, and high disease burden subgroups and randomly assigned 1:1 to receive either thermal ablation (experimental group) or surgical resection (control group) of all target colorectal liver metastases using the web-based module Castor electronic data capture with variable block sizes of 4, 6, and 8. Although at the operator's discretion, a minimally invasive approach in both treatment groups was recommended. The primary endpoint was overall survival, assessed in the intention-to-treat population. A hazard ratio (HR) of 1·30 was considered the upper limit of non-inferiority for the primary endpoint. A preplanned interim analysis with predefined stopping rules for futility (conditional power to prove the null hypothesis <20%) and early benefit (conditional power >90%, superior safety outcomes for the experimental group, and no difference or superiority regarding local control for the experimental group) was done 12 months after enrolment of 50% of the planned sample size. Safety was assessed per treatment group. This trial is registered with ClinicalTrials.gov, NCT03088150.

Findings Between Aug 7, 2017, and Feb 14, 2024, 300 patients were randomly assigned to the experimental group (n=148, 100 male [68%] and 48 female [32%]; median age 67·9 years [IQR 29·2–85·7]) or to the control group (n=148, 107 male [72%] and 41 female [28%]; median age 65·1 [IQR 31·4–87·4]); four patients (two in each treatment group) were excluded after randomisation because they were found to have other disease pathology. Median follow-up at the prespecified interim analysis was 28·9 months (IQR 0·3–77·8). The trial was stopped early for meeting the predefined stopping rules: (1) a conditional likelihood to prove non-inferiority for overall survival of 90·5% (median overall survival not reached in both groups; HR 1·05; 95% CI 0·69–1·58; p=0·83), (2) a non-inferior local control (median local control not reached in both groups; HR 0·13, 95% CI 0·02–1·06; p=0·057), and (3) a superior safety profile for the experimental group. Patients in the experimental group had fewer adverse events than those in the control group (28 [19%] *vs* 67 [46%]; p<0·0001). Serious adverse events occurred in 11 (7%) of 148 patients in the experimental group and 29 (20%) of 146 in the control group, mostly periprocedural haemorrhage requiring intervention (one [1%] *vs* eight [5%]), and infectious complications requiring intervention (six [4%] *vs* 11 [8%]). There were no treatment-related deaths in the experimental group and three treatment-related deaths (2%) in the control group (two due to postoperative cardiac complications and one due to sepsis and liver failure).

Lancet Oncol 2025; 26: 187–99

Published Online January 20, 2025 https://doi.org/10.1016/S1470-2045(24)00660-0

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Interpretation **The assumption that thermal ablation should be reserved for unresectable colorectal liver metastases requires re-evaluation and the preferred treatment should be individualised and based on clinical characteristics and available expertise.**

Funding **Medtronic-Covidien.**

Introduction

The current standard of care for treating colorectal liver metastases is surgical resection with reported 10-year survival rates of 18–24%.[1–3] Over the last two decades, thermal ablative methods, especially radiofrequency ablation and microwave ablation, have gained popularity as adjuncts to surgical resection or as a standalone treatment when complete surgical removal of all metastatic sites is not feasible.[4,5] More specifically, for patients with an impaired performance status, high comorbidity score, history of extensive abdominal surgery, and for patients with anatomically unresectable small-size tumours, thermal ablation seems to offer a safe, effective, and parenchyma-sparing means to eradicate disease.[4,6]

Although both surgical and ablation techniques have improved, the advances in local effectiveness and the ease of repeating ablations in case of local tumour progression following percutaneous ablations have instigated the discussion of whether thermal ablation could serve as an alternative to surgical resection for small-size resectable colorectal liver metastases.[7] In the absence of globally adopted resectability and ablatability criteria, differences in clinical practice have emerged as some centres resect nearly all colorectal liver metastases, whereas others have gradually shifted towards ablating the majority of small-size metastases.

Several meta-analyses have previously shown thermal ablation to be inferior to surgical resection for overall survival.[4,6] However, these analyses were at risk of residual bias by comparing surgical candidates to non-surgical patients. More recent studies report similar survival outcomes between the two approaches, revitalising this debate.[8–11]

The international, phase 3, randomised controlled COLLISION trial assessed the potential non-inferiority of thermal ablation compared with surgical resection, in terms of overall survival, in patients with small-size resectable colorectal liver metastases (≤3 cm).

Methods

Study design and participants

The COLLISION trial, accommodated by the Dutch Colorectal Cancer Group (DCCG), recruited patients from 14 centres (eight academic and six non-academic): 12 in the Netherlands, one in Belgium, and one in Italy (appendix p 8). The study protocol (appendix pp 19–143) was granted approval by the Institutional Review Board of the Amsterdam UMC (2016.561) and the participating

Research in context

Evidence before this study

We used Cochrane systematic review methods to identify studies and searched MEDLINE, Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, CENTRAL). No time limit was used. For patients with colorectal liver metastases, several prior meta-analyses based on retrospective comparative series labelled thermal ablation inferior to surgical resection in terms of overall survival. However, these analyses might have been subject to residual bias, as the included studies most often compared surgical candidates to patients who did not qualify for surgery. Several more recent comparative retrospective series and one registry-controlled prospective series (MAVERRIC) reported similar survival outcomes. Surgical resection and thermal ablation have transitioned from invasive open procedures to minimally invasive laparoscopic or robot-assisted approaches, significantly reducing procedural risks. The advances in local effectiveness and the ease of repeating ablations in case of local tumour progression have instigated the discussion whether thermal ablation could serve as an alternative to surgical resection for small-size resectable colorectal liver metastases.

Added value of this study

The COLLISION trial was stopped early for meeting predefined criteria for early benefit. The trial demonstrated a high likelihood (conditional power >90%) of proving non-inferiority regarding overall survival, non-inferior local control, and fewer complications with thermal ablation compared with surgical resection for small-size colorectal liver metastasis (≤3 cm).

Implications of all the available evidence

Both thermal ablation and surgical resection should be considered effective treatment options for patients with colorectal liver metastases. The assumption that thermal ablation should only be used for unresectable colorectal liver metastases needs to be reconsidered and our results advocate a more individualised approach to treatment. Clinicians should consider offering both treatment options and tailor the choice to the individual patient's needs.

centres. All patients provided written informed consent. All procedures were performed following the guidelines for Good Clinical Practice and the Declaration of Helsinki.

Adult patients (aged ≥18 years) with one to ten target colorectal liver metastases, defined as ablatable and resectable, according to the local multidisciplinary tumour board, and of 3 cm or less in diameter, were considered for participation. A limited number (<50%) of concomitant unablatable or unresectable tumours was allowed, as long as all unablatable colorectal liver metastases were considered resectable and, vice versa, all unresectable colorectal liver metastases were considered ablatable (non-target tumours). We excluded patients with extrahepatic metastases, an Eastern Cooperative Oncology Group status (ECOG) greater than 2, and a history of locoregional liver treatment. Patients also had to have an American Society of Anesthesiologists (ASA) grade of 1–3, a life expectancy of at least 12 weeks, and adequate bone marrow, liver, and renal function. Detailed inclusion and exclusion criteria and pre-procedural work-up are described in the study protocol and have been previously published.[12]

Potential participants were first discussed in local multidisciplinary tumour boards. Hereafter, the treating physicians shared anonymous patients' medical history, diagnostic examinations, along with the treatment plans if randomised to thermal ablation and to surgical resection, with a centralised review panel. This review panel consisted of 31 interventional radiologists and 32 hepatobiliary surgeons with a minimum of 5 years of relevant working experience. Consensus was reached when two interventionalists and two hepatobiliary surgeons, unaffiliated with the patient's clinical care, agreed on the ablatability and resectability of the target tumours and feasibility of both local treatment plans. Details concerning the expert panel are provided in the appendix (p 5) and the protocol. Two exclusion criteria were added to the protocol (version 2.2; April 6, 2021) after recruitment had already started: (1) the presence of one or two small-size and deep-seated colorectal liver metastases requiring major hepatectomy, for which thermal ablation was preferred, and (2) two-stage resections with portal vein embolisation, for which a single-stage resect-and-ablate procedure was preferred.

Eligible patients were stratified per centre and according to their disease load into three subgroups: low disease burden (subgroup A), intermediate disease burden (subgroup B), or high disease burden (subgroup C; appendix pp 5, 9). Low disease burden (subgroup A) was defined as having one to three colorectal liver metastases of 3 cm or less in diameter, all suitable for both thermal ablation and surgical resection (target tumours). Intermediate disease burden (subgroup B) was defined as having a total of four to ten colorectal liver metastases or one to three colorectal liver metastases with at least one non-target tumour. The definition of high-disease burden (subgroup C) was the same as subgroup B, but with the additional condition that, when randomly assigned to surgical resection, major hepatectomy would be necessary. In subgroups B and C, concomitant non-target tumours were registered as such before randomisation and they were disregarded in comparative analyses that address the local effectiveness of both techniques. Participants in subgroup B and C who underwent an open (laparotomic) procedure, were reassessed for eligibility after surgical inspection and intraoperative ultrasound and subsequently randomly assigned intraoperatively. The rationale for this was to minimise the number of randomly assigned patients receiving no local treatment or crossing over. Participants were excluded before randomisation if a radical procedure was no longer considered safe or feasible, more than ten colorectal liver metastases were detected, extrahepatic metastases were identified (eg, peritoneal metastases), no target tumours remained, or the number of target tumours was less than 50% of all colorectal liver metastases.

Randomisation and masking

After stratification per centre and into the three disease burden subgroups, patients were randomly assigned 1:1 to the experimental group or the control group, undergoing thermal ablation or surgical resection of all appointed target colorectal liver metastases, using the web-based module Castor electronic data capture with variable block sizes of 4, 6, and 8. Study staff and participants were not masked to treatment allocation.

Procedures

Potential candidates were registered in the trial database and routine pre-procedural assessments consisted of an anaesthetic review, complete blood count, and a contrast-enhanced CT of the chest and abdomen, combined with either a liver contrast-enhanced MRI scan or an [^{18}F] fluorodeoxyglucose ([^{18}F]FDG)-PET-CT scan, or both, according to local protocols. Sex was registered using the electronic patient database. We did not collect data on ethnicity or race.

For resection, the choice of an open, laparoscopic, or robot-assisted approach was at the discretion of the treating surgeons. The ablation device, the open, laparoscopic, or percutaneous approach, and the method of needle guidance was at the discretion of the treating physicians; confirmation software was recommended but not obligatory. Ablation procedures were performed according to the manufacturer's instructions for use. The study group adhered to predefined resectability and ablatability criteria.[13] Details are provided in the protocol.

In accordance with national and international guidelines, follow-up consisted of cross-sectional imaging and laboratory tests including carcinoembryonic antigen every 3–4 months for the first year and every 6 months thereafter.[1,14] Imaging included a

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See Online for appendix

contrast-enhanced CT of the chest and abdomen and either upper abdominal contrast enhanced MRI or ^{18}F-FDG PET-CT scans. Additionally, quality of life and health-economics related questionnaires (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 [EORTCQLQ-C30] version 3, EQ5D version 1, and Productivity and Disease Questionnaire [PRODISQ] version 1) were completed at baseline, every 3 months for the first year, and every 6 months thereafter accordingly.

Adverse events were monitored continuously throughout the study and assessed according to the common terminology criteria for adverse events (CTCAE) version 5.0.[15] All serious adverse events where reported to the competent authorities within 7 days in accordance with EU regulatory requirements. Patients could withdraw consent at any time, and participation was discontinued if histopathology confirmed the absence of the assessed disease. To assess survival, follow-up continued for randomly assigned patients who did not receive the allocated treatment or for whom follow-up imaging was no longer performed at the request of the patient or their treating physician.

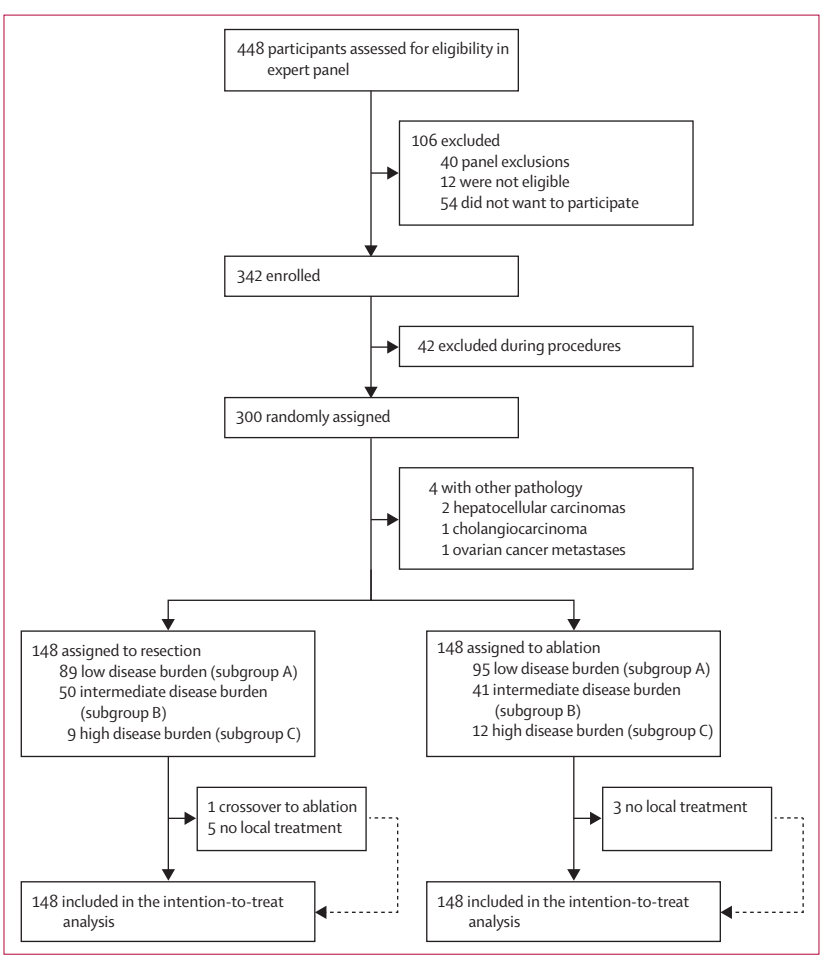

Figure 1: **Trial profile**

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to the date of death from any cause. Secondary outcomes were safety, defined as the rate of adverse events and serious adverse events; local tumour progression-free survival, defined as the time from randomisation to the time of any local tumour progression per patient treated (per-patient analysis) and the time of local tumour progression of appointed target colorectal liver metastasis per tumour treated (per-tumour analysis); distant tumour progression-free survival, defined as the time from randomisation to the time of disease progression distant from the local treatment zones; loss of local control, defined as the time elapsed from randomisation until the first detection of locally recurrent disease that was not retreated with surgery or ablation, analysed both per patient treated (per-patient analysis) and per target colorectal liver metastasis (per-tumour analysis); local control, defined as the percentage of patients (per-patient analysis) and tumours (per-tumour analysis) in whom the target tumours were eventually eradicated, including repeat treatments regardless of the type of retreatment; and length of hospital stay, defined as the number of nights spent in the hospital.[16] A detailed assessment of the other prespecified secondary endpoints (quality-of-life, pain assessment [on visual analogue scale questionnaires], and cost-effectiveness) will be described in a separate publication.

Statistical analysis

This trial was powered to assess potential non-inferiority of thermal ablation over surgical resection for the primary endpoint overall survival. Hazard ratios (HRs) were adjusted for centre and disease burden stratification. Based on the results of a preceding systematic review and meta-analysis of retrospective comparative series, used as background data, and compliant to the European Medicines Agency guideline on the choice of the non-inferiority margin, an HR of 1·30 was considered the upper limit of non-inferiority for the primary endpoint overall survival.[4,7,17,18] The calculated sample size was 618 patients (two-sided significance of 5% at 80% power, and assuming a 10% drop-out rate and 3% loss to follow-up). For the secondary endpoints distant tumour progression-free survival, local tumour progression-free survival, and local control, the non-inferiority margin of 1·30 for the HR was used, whereas for safety the potential superiority of the experimental group was assessed.[17] A preplanned interim analysis with predefined stopping rules for futility (conditional power to prove the null-hypothesis <20%) and early benefit (conditional power >90%, superior safety outcomes for the experimental group, and no difference or superiority regarding local control for the experimental group) was conducted 12 months after having included 50% of the original sample size (n=309). The criteria to cease the trial early for proven

	Experimental group (n=148)	Control group (n=148)
Patient-related characteristics		
Age, years	67·9 (29·2–85·7)	65·1 (31·4–87·4)
Sex		
Male	100 (68%)	107 (72%)
Female	48 (32%)	41 (28%)
ASA score		
2	102 (69%)	121 (82%)
3	46 (31%)	27 (18%)
Charlson's comorbidity index		
None	53 (36%)	74 (50%)
Minor	69 (47%)	70 (47%)
Intermediate	26 (18%)	4 (3%)
BMI, kg/m²	26·5 (18·6–42·7)	26·1 (17·2–45·5)
Disease-related characteristics		
Primary tumour		
Right-sided	33 (22%)	40 (27%)
Left-sided	57 (39%)	50 (34%)
Rectum	58 (39%)	58 (39%)
T stage		
1	4 (3%)	3 (2%)
2	22 (15%)	15 (10%)
3	93 (63%)	97 (66%)
4	29 (20%)	33 (22%)
N stage		
0	55 (37%)	33 (22%)
1	61 (41%)	79 (53%)
2	32 (22%)	36 (24%)
M stage (at diagnosis of primary tumour)		
0	71 (48%)	79 (53%)
1	77 (52%)	69 (47%)
Extrahepatic disease at diagnosis of colorectal liver metastases		
No	147 (99%)	148 (100%)
Yes	1 (1%)	0
Molecular profile		
RAS status		
Wild type	25 (53%)	24 (47%)
Mutated	22 (47%)	27 (53%)
Missing	101	97
BRAF status		
Wild type	41 (89%)	45 (88%)
Mutated	5 (11%)	6 (12%)
Missing	102	97
MSS or MSI status		
MSS	98 (100%)	143 (99%)
MSI	0	1 (1%)
Missing	50	4
Subgroup		
Subgroup A (low disease burden)	95 (64%)	89 (60%)
Subgroup B (intermediate disease burden)	41 (28%)	50 (34%)
Subgroup C (high disease burden)	12 (8%)	9 (6%)
Procedure-related characteristics		
Induction chemotherapy		
No	118 (80%)	112 (76%)
Yes	30 (20%)	36 (24%)
Capecitabine	2 (1%)	2 (1%)
CAPOX	3 (2%)	2 (1%)
CAPOX-B	21 (14%)	23 (16%)
FOLFOX-B	2 (1%)	2 (1%)
FOLFIRI-B	1 (1%)	2 (1%)
FOLFOXIRI-B	1 (1%)	4 (3%)
Missing	0	1
Induction chemotherapy cycles		
Median (range)	6 (3–12)	6 (2–10)
Procedure details		
Resection alone	0	90 (61%)
Ablation alone	118 (80%)	1 (1%)*
Resection with ablation	27 (18%)†	52 (35%)‡
No local treatment	3 (2%)	5 (3%)
Approach§		
Percutaneous	84 (57%)	1 (1%)*
Laparoscopic or robotic	10 (7%)	69 (47%)
Open	54 (36%)	76 (51%)

(Table 1 continues in next column)

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benefit were based on the Declaration of Helsinki's ethical principles, prioritising minimisation of harm, ensuring participant welfare and safety, and fulfilling the fiduciary duty to act in the best interests of participants when the principle of equipoise is potentially violated.

The post-hoc cumulative incidence function analysis was performed using the Fine and Gray subdistribution hazard model for competing risks (appendix p 6). Patients were excluded from all analyses if histopathology confirmed that the liver lesions were not colorectal liver metastases. For the analysis of overall survival, distant tumour progression-free survival, local tumour progression-free survival, and local control, all participants with colorectal liver metastases were evaluated according to the intention-to-treat principle, wherein patients who ultimately did not receive local treatment or were treated according to the other treatment group (crossover) were retained in the original group to which they were allocated. Response evaluation was based on available radiology reports, with central review conducted to resolve any discrepancies or ambiguities. Adverse events were recorded only for patients who underwent local treatment, retaining crossovers in their originally

	Experimental group (n=148)	Control group (n=148)
(Continued from previous column)		
Anaesthetic management§		
General anaesthesia	111/146 (76%)	146/146 (100%)
Propofol sedation	37/146 (25%)	0
Number of colorectal liver metastases		
Median	2 (1–10)	2 (1–10)
1	56 (38%)	56 (38%)
2–5	68 (46%)	68 (46%)
>5	24 (16%)	24 (16%)
Tumour-related characteristics		
Colorectal liver metastases type		
Target¶	349/447 (78%)	304/446 (68%)
Non-target¶	98/447 (22%)	142/446 (32%)
Size, mm (range)	13 (3–30)	14 (2–30)

Data are median (IQR) or n (%), unless otherwise indicated. ASA=American Society of Anaesthesiologists. CAPOX=oxaliplatin and capecitabine. CAPOX-B=oxaliplatin and capecitabine plus bevacizumab. FOLFOX-B=folinic acid, fluorouracil, and oxaliplatin plus bevacizumab. FOLFIRI-B=fluorouracil, folinic acid, and irinotecan plus bevacizumab. FOLFOXIRI-B=fluorouracil, leucovorin, oxaliplatin, and irinotecan plus bevacizumab. MSI=microsatellite instability. MSS=microsatellite stability. NA=not applicable or not routinely established. *Crossover. †Patients who, concomitantly with the thermal ablation of appointed target colorectal liver metastases, also had at least one unablatable non-target colorectal liver metastases that was resected. ‡Patients who, concomitantly with the resection of appointed target colorectal liver metastases, also had at least one unresectable non-target colorectal liver metastases that was ablated. §Two patients were randomly assigned, but their procedures were cancelled due to rapid disease progression. ¶Target: resectable and ablatable; non-target: unresectable or unablatable.

Table 1: **Baseline characteristics**

assigned group. Three post-hoc sensitivity analyses were performed: (1) to compare the local tumour progression-free survival and local control in patients treated with percutaneous, laparoscopic and open ablations (in the experimental arm); (2) to compare the local tumour progression-free survival and local control in patients treated with percutaneous ablation (experimental arm) versus patients treated with (robot) laparoscopic resection (control arm); and (3) to assess the differences in local tumour progression-free survival and local control per institution in patients treated with ablation (experimental arm). Furthermore the pathology-based R0 and R1 rates (defined as margins <1 mm *vs* ≥1 mm) for the resected target tumours were compared with the imaging-based A0 and A1 rates (defined as margins <5 mm *vs* ≥5 mm) for the ablated target tumours.

Baseline-related and procedure-related characteristics were summarised using descriptive statistics. The Kaplan–Meier curve with log-rank (Mantel–Cox) test was used to estimate overall survival, local tumour progression-free survival, distant tumour progression-free survival, and local control.[16] The Cox proportional hazards model was used to calculate HRs and 95% CIs. The proportional hazards assumption was based on visual inspection of the Kaplan–Meier estimates of overall survival. In the overall survival analysis, in case of loss-to-follow-up, the date of last follow-up was censored. In the analysis of distant progression-free survival, deaths without distant progression (competing risk) were censored. In the analysis of local tumour progression-free survival, deaths without local tumour progression (competing risk) were censored. In the analysis of local tumour control, deaths without loss of local tumour control (competing risk) were censored, and the presence of scattered multifocal or extrahepatic, or both, was considered a competing risk. Adverse events were noted per patient, ranking the highest grade complication, and analysed using the Fisher's exact test. CTCAE grade 3–5 complications were considered serious adverse events. The Mann–Whitney U test was performed to analyse length of hospital stay. Differences were considered statistically significant when $p<0·05$. As preplanned subgroup analyses, the differences between ablation and resection regarding overall survival, distant tumour progression-free survival, local tumour progression-free survival, and local control were also assessed for the three disease burden subgroups separately. SPSS software (version 26.0) and the R software package (version 4.0.3) were used to perform statistical analyses. All results were reported according to the CONSORT statement.[19] A web-based module (Castor EDC) was used to collect data. This trial is registered with ClinicalTrials.gov number, NCT03088150.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 7, 2017, and Feb 14, 2024, a total of 448 patients were assessed for eligibility by the reviewing panel; 40 were considered ineligible for trial participation according to the panel, 12 eventually failed eligibility after initial panel approval and 54 patients did not want to participate. 12 months after having recruited 50% of the original sample size, 342 patients were included in the pre-planned interim analysis. Of these, 42 patients were excluded after reassessment in the operating theatre, before random assignment to either the experimental group or the control group, due to detection of disease beyond the inclusion criteria. Finally, 300 patients were randomly assigned to the experimental group (150 patients) or the control group (150 patients; figure 1). Four randomly assigned patients (two in each treatment group) were excluded because histopathological examination confirmed the liver tumours to represent hepatocellular carcinomas (two patients), cholangiocarcinoma (one patient), and ovarian carcinoma metastasis (one patient). Of the 148 patients in the experimental group, 100 were male (68%) and 48 were female (32%) with a median age of 67·9 years

(IQR 29·2–85·7; table 1). Of the 148 patients in the control group, 107 were male (72%) and 41 were female (28%) with a median age of 65·1 years (IQR 31·4–87·4). One patient, who was randomly assigned to surgical resection, ultimately underwent percutaneous ablation (crossover). Of the 142 patients who underwent resection in the control group, one patient received an extended right hemihepatectomy, ten patients a right hemihepatectomy, three patients a left hemihepatectomy, 14 patients underwent a bisegmentectomy of segments 2 and 3, five patients a posterior sectionectomy of segments 6 and 7, and two patients a right trisegmentectomy; the remaining 107 patients underwent non-anatomical wedge resections. 52 patients (37%) had at least one unresectable non-target colorectal liver metastases that was ablated. Of the 145 patients who underwent thermal ablation, 134 were treated with microwave ablation and 11 with radiofrequency ablation; after May 11, 2021, radiofrequency ablation procedures were no longer done in the trial. Of the 27 patients in the experimental group who underwent resection in conjunction with the ablation, one patient received a hemihepatectomy, four underwent a bisegmentectomy of segments 2 and 3, and 22 underwent additional non-anatomical wedge resections. 27 patients (18%) had at least one unablatable non-target colorectal liver metastases that was resected. After consultation with the trial steering committee, the Data Safety Monitoring Board and the Institutional Review Board, recruitment was halted on March 1, 2024.

In the preplanned interim analysis, after a median follow-up of 28·9 months (IQR 0·3–77·8), 90 (30%) of 296 patients had died; 47 (32% of 148) in the experimental group and 43 (29% of 148) in the control group. No evidence for a difference in overall survival was found (median overall survival not reached in both groups; HR 1·05; 95% CI 0·69–1·58; p=0·83; figure 2A). In the total study cohort, overall survival

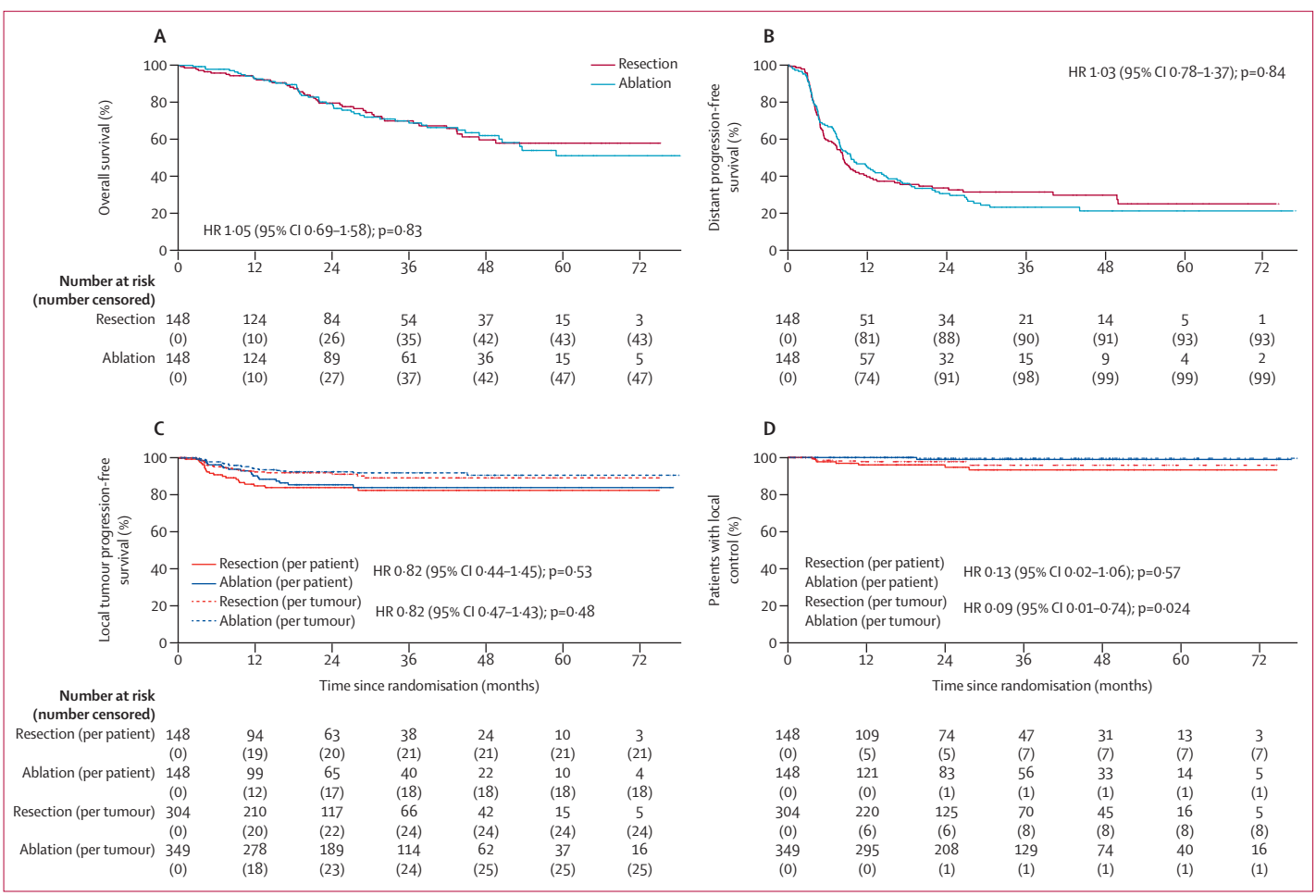

Figure 2: **Kaplan–Meier curves for survival outcomes**
(A) Overall survival, (B) distant progression-free survival, (C) local tumour progression-free survival, and (D) local control with Cox regression values. (A) Overall comparison log-rank (Mantel–Cox) test, p=0·83. (B) Overall comparison log-rank (Mantel–Cox) test, p=0·84. (C) Per-patient analysis: overall comparison log-rank (Mantel–Cox) test, p=0·53; per-target tumour analysis: overall comparison log-rank (Mantel–Cox) test, p=0·47. (D) Per-patient analysis: overall comparison log-rank (Mantel–Cox) test, p=0·025; per target tumour analysis: overall comparison log-rank (Mantel–Cox) test, p=0·0050. HR=hazard ratio.

rates were 92·8% (95% CI 89·9–95·7) at 1 year, 79·1% (74·0–84·2) at 2 years, and 54·5% (46·5–62·5) at 5 years. In the experimental group, survival rates were 92·7% (91·2–94·1) at 1 year, 78·5% (71·2–85·8) at 2 years, and 51·2% (39·4–63·0) at 5 years. In the control group, survival rates were 92·9% (91·3–94·4) at 1 year, 79·6% (77·0–82·3) at 2 years, and 58·0% (53·4–62·9) at 5 years. The conditional power to prove non-inferiority of thermal ablation compared with surgical resection, for the primary endpoint overall

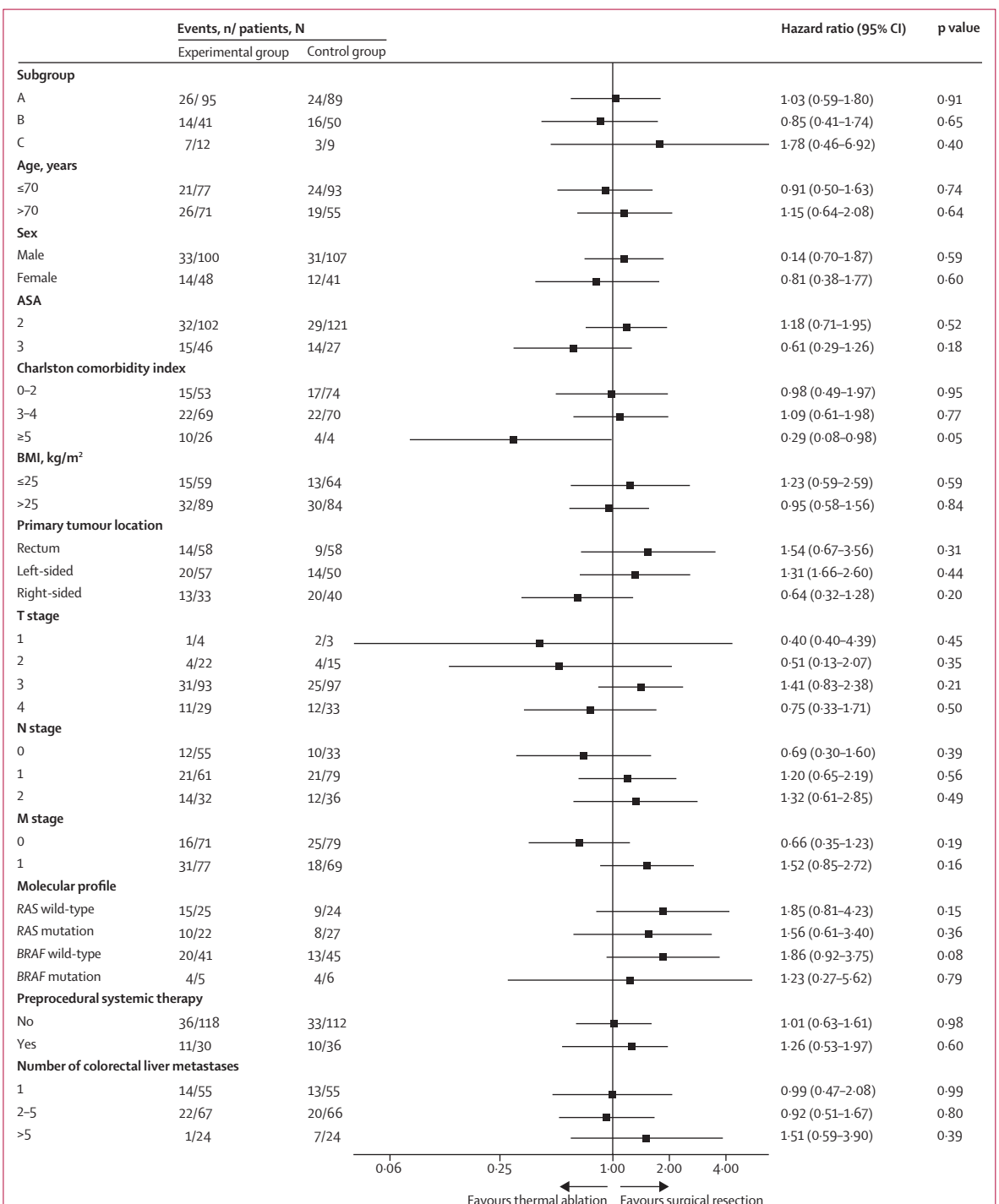

Figure 3: **Univariate subgroup Cox regression analyses of overall survival**
ASA=American Society of Anaesthesiologists score. NA=not available.

survival, was 90·5%, assuming 6 more years of recruitment based on current accrual (conditional power calculation is detailed in the statistical analysis plan; appendix pp 144–165). The proportional hazards assumption was met. Subgroup analyses showed no significant differences in overall survival between the experimental group and the control group in any subgroup (figure 3, appendix pp 10–15).

Details regarding adverse events are shown in tables 2–4 and the appendix (p 17). Two patients in the control group were excluded from the adverse events analysis, since their procedures were cancelled due to rapid disease progression. Three patients in each group who were already under general anaesthesia or deep sedation, but did not receive local treatment, were included in this assessment. All-cause 90-day mortality was 1% (one patient) in the experimental group versus 2% (three patients) in the control group (tables 2, 3). Treatment-specific 90-day mortality was recorded in no patients in the experimental group versus three (2%) patients in the control group. The total number of adverse events was significantly higher in the control group than in the experimental group (in 67 [46%] of 146 patients *vs* 28 [19%] of 148 patients; p<0·0001; table 4). Additionally, both the number of adverse events for low-grade (CTCAE grade 1–2) and high-grade adverse events (CTCAE grade 3–5) favoured the experimental group (p=0·004 and p=0·004, respectively). Serious adverse events occurred in 11 (7%) of 148 patients in the experimental group and 29 (20%) of 146 in the control group, mostly periprocedural haemorrhage requiring intervention (one [1%] *vs* eight [5%]), and infectious complications requiring intervention (six [4%] *vs* 11 [8%]).

Length of hospital stay differed significantly between the two groups, with a median duration of 4 days (IQR 1–36) in the control group versus 1 day (IQR 1–44) in the experimental group (p<0·0001; appendix p 17).

No difference between the treatment groups was found concerning distant tumour progression-free survival (median 8·4 months [95% CI 6·8–9·9] in the control group *vs* 9·6 months [6·3–12·8] in the experimental group; HR 1·03; 95% CI 0·78–1·37; p=0·84; figure 2B). Overall comparison of local tumour progression-free survival per-patient and per-tumour between the two study groups showed no significant differences. Median local tumour progression-free survival was not reached in both groups (HR 0·82, 95% CI 0·44–1·45, p=0·53 for the per-patient analysis and 0·82, 0·47–1·43, p=0·48 for the per-tumour analysis; figure 2C). Median loss of local tumour control was not reached in both groups. For the per-patient local control analysis, the experimental group was non-inferior (HR 0·13, 95% CI 0·02–1·06; p=0·057) and, for per-tumour local control, the experimental group was superior (HR 0·09, 95% CI 0·01–0·74; p=0·024; figure 2D) to the control group. At final analysis, local tumour progression was reported in 18 (12%) of 148 patients and 25 (7%) of 349 target tumours in the experimental group versus 21 (14%) of 148 patients and 24 (8%) of 304 target tumours in the control group (appendix p 18).

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Death due to colon perforation*	..	..	..	..	1
Sepsis, ileus, aspiration pneumonia requiring ICU stay	..	..	..	1	..
Postoperative haemorrhage requiring relaparotomy	..	..	..	1	..
Liver abscess requiring intervention	..	..	3	..	..
Acute kidney failure requiring dialysis	..	..	1	..	..
Biliary tract injury requiring percutaneous intervention	..	..	2	..	..
Infection following open procedure requiring antibiotics	..	..	1	..	..
Infected liver infarction and endoprosthesis requiring antibiotics	..	..	1	..	..
Peri-procedural haemorrhage requiring tranexamic acid	..	1	..	..	..
Pneumonia	..	2	..	..	..
Biloma	..	1	..	..	..
Herniation of right diaphragm	..	1	..	..	..
Fever, fatigue, pain, dyspnoea, or obstipation	1	3	..	..	..
Peri-procedural haemorrhage (no intervention)	3	..	..	..	..
Antenna tip fracture (remained in situ)	2	..	..	..	..
Lobar atelectasis	1	..	..	..	..
At least 4 days of itch due to epidural anaesthesia	1	..	..	..	..
Pneumothorax (no intervention)	1	..	..	..	..
Total	9	8	8	2	1

Data are reported as number of patients. ICU=intensive care unit. *Not related to the study procedure.

Table 2: **Adverse events in the thermal ablation group (n=148)**

In the experimental group, 16 patients with a total of 16 recurring tumours were successfully retreated: 13 with ablation and three with resection; two patients with two locally progressed tumours did not (at the time of data analysis) receive local retreatment. In the control group, seven patients with seven recurring tumours were successfully retreated: six with thermal ablation, one with resection; 15 patients with a total of 17 locally progressed tumours did not receive resection or ablation (at the time of data analysis). The post-hoc cumulative incidence analysis of competing risks showed no significant differences between the two treatment groups for distant tumour progression-free survival, local tumour progression-free survival, and local control (appendix p 16).

In the control (resection) group, the pathology-based R1 rate (<1 mm margins) for resected target tumours was 33 (12%) of 274 tumours; out of which 12 (36%) tumours showed local tumour progression during follow-up. Subsequently, pathology-based R0 resections (≥1 mm margins) correctly reflected the absence of resection plane recurrence in 230 (95%) of 241 resected target tumours. In the experimental (thermal ablation) group, the imaging-based A1 rate (<5 mm margins) for ablated tumours was 17 (5%) of 322, of which eight (47%)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Death due to myocardial infarction	..	..	..	..	1
Death due to sepsis, liver failure	..	..	..	..	1
Death due to cardiac arrest	..	..	..	..	1
Multi-organ failure requiring ICU stay	..	..	..	1	..
Respiratory insufficiency due to pneumonia requiring ICU stay	..	..	..	1	..
Peri-procedural haemorrhage with hemodynamic shock requiring intervention	..	..	..	2	..
Closed loop ileus requiring diagnostic laparoscopy	..	..	..	1	..
Tension pneumothorax requiring drain	..	..	..	1	..
Liver abscess, acute kidney injury, hospital acquired pneumonia, delirium, or parotitis	..	..	..	1	..
Liver abscess requiring intervention	..	..	3	..	..
Pneumonia requiring antibiotics and prolonged hospital admission	..	..	4	..	..
Hospital acquired pneumonia, COVID-19, or wound infection requiring drainage	..	..	1	..	..
Pulmonary embolism	..	..	1	..	..
Peri-procedural haemorrhage requiring intervention	..	..	6	..	..
Transient ischaemic attack	..	..	1	..	..
Pain, nausea, and free air requiring re-laparotomy	..	..	1	..	..
Post-operative pneumothorax requiring pleura catheter	..	..	1	..	..
General malaise requiring admission	..	..	1	..	..
Diaphragm injury	..	1	..	..	..
Allergic skin rash requiring medication	..	1	..	..	..
Retention bladder	..	1	..	..	..
Cardiac decompensation requiring medication	..	1	..	..	..
Ileus requiring prolonged stay	..	1	..	..	..
Gastroparesis	..	2	..	..	..
Liver abscess requiring antibiotics	..	1	..	..	..
Pneumonia	..	1	..	..	..
Cellulitis requiring antibiotics	..	1	..	..	..
Fever, fatigue, pain, dyspnoea, or obstipation	17	6	..	..	..
Peri-procedural haemorrhage (no intervention)	1	..	..	..	..
Morphine intoxication	1	..	..	..	..
Surgical biliary tract injury requiring suction and compression	1	..	..	..	..
Cystitis	1	..	..	..	..
Biloma	1	..	..	..	..
Total	22	16	19	7	3

Data are reported as number of patients. ICU=intensive care unit.

Table 3: **Adverse events in the surgical resection group (n=146)**

	Experimental group (n=148)	Control group (n=146)*	p value
Adverse events	28 (19%)	67 (46%)	<0·0001†
Grade 1	9 (6%)	22 (15%)	..
Grade 2	8 (5%)	16 (11%)	..
Grade 3	8 (5%)	19 (13%)	..
Grade 4	2 (1%)	7 (5%)	..
Grade 5	1 (1%)	3 (2%)	..
All grades	..	..	<0·0001‡

Data are n (%). CTCAE=Common Terminology Criteria for Adverse Events. *Two patients were randomly assigned, but their procedures were cancelled due to rapid disease progression. †Fisher's Exact test. ‡Pearson's χ^2 test.

Table 4: **Adverse events by CTCAE grade**

recurred within the follow-up period. Consequently, imaging-based A0 ablations (≥5 mm margins) correctly reflected the absence of local tumour progression in 290 (95%) of 305 ablated target tumours.

The results of the three post-hoc sensitivity analyses can be found in the appendix (p 7). Based on the results of the interim analysis, the trial was stopped early for meeting the predefined stopping rules: a conditional likelihood to prove non-inferiority for the primary endpoint overall survival of more than 90% (91%), a superior safety profile, and a non-inferior local control for the experimental group.

Discussion

The trial stopped early for meeting predefined criteria for early benefit: a high likelihood (conditional power >90%) of proving non-inferiority regarding overall survival, a non-inferior local control, and fewer adverse events with thermal ablation compared with surgical resection for small-size colorectal liver metastases (≤3 cm). The decision to halt recruitment was substantiated by increasingly difficult accrual due to evolving medical insights, as continuing was deemed unethical and would likely extend the trial by at least 6 more years. No evidence for a difference in overall survival between the treatment groups was found.

These outcomes challenge previous conclusions from meta-analyses favouring surgical resection over thermal ablation in patients with colorectal liver metastases.[6,20,21] This discrepancy highlights the effect of residual confounding in many of those retrospective comparative studies, as thermal ablation was typically only offered when surgical resection was not a viable option. A trend towards similar outcomes for the more recent series was previously postulated.[4] Karanicolas and colleagues[8] and Faitot and colleagues[10] found single-stage resection plus ablation to be associated with improved perioperative outcomes without compromising survival, compared with two-stage resections. Eltawil and colleagues[9] found a similar survival rate, without an increased risk of local failure for thermal ablation compared with surgery. Hof and colleagues,[11] Tinguely and colleagues,[22] and Huang and colleagues[23] reported similar overall survival rates between thermal ablation and surgery. Van de Geest and colleagues[24] showed fewer adverse events and a comparable overall survival for thermal ablation, suggesting it to be a safe alternative for suboptimal surgical candidates. The non-randomised registry-controlled MAVERRIC trial also found a comparable overall survival, lower morbidity, and wider options regarding retreatments with thermal ablation compared with surgical resection.[25]

The superior safety profile of thermal ablation aligns with previous systematic reviews and meta-analyses. Meijerink and colleagues[4] and van Amerongen and colleagues[6] reported risk ratios of 0·44–0·47 (95% CI 0·26–0·78; p=0·003 and p=0·002, respectively), with adverse events in 25% of surgical procedures versus 10–12% following ablative procedures. The shorter length of hospital stay for thermal ablation is also consistent with earlier studies.[4,6,20,21]

The R1 rate of 12% reported in our study is low compared with the rate described in the two largest studies in the literature; 17% reported by Sadot and colleagues and 24% reported by Hamady and colleagues.[26,27] This discrepancy might stem from our focus on small-size (≤3cm) colorectal liver metastases. R1 and A1 treatments resulted in local tumour progression rates of 36% and 47%. Pathology-based R0 resections (≥1 mm margins) and imaging-based A0 ablations (≥5 mm margins) reflected complete treatment in 95% of cases each.

An earlier attempt to compare thermal ablation with surgical resection stopped prematurely due to treatment preferences and misconceptions about eligibility (LAVA ISRCTN52040363).[28] The ongoing NEW-COMET trial (NCT05129787) compares the 12-month local tumour progression rate after thermal ablation versus surgical resection and the HELARC trial (NCT02886104) compares simultaneous resection of the primary tumour and liver metastases to staged resection of the primary tumour and percutaneous thermal ablation of the colorectal liver metastases.

Several factors contributed to study accrual. First, the group established resectability and ablatability criteria based on a structured Delphi consensus process, aligning participating physicians.[13] Second, by transparently asking surgical panellists only about resectability and interventional panellists only about ablatability, the risk of prejudice was reduced. Third, allowing local physicians to determine the specific approach (laparotomic, robotic or laparoscopic, or percutaneous) facilitated consensus.

Nonetheless, recruitment remained challenging due to persistent biases, assumptions, and evolving medical insights. Surgical panellists often preferred single-stage resect and ablate procedures over two-stage resections and started rejecting major hepatectomies for solitary deep-seated colorectal liver metastases. The presence of ablatable solitary deep-seated colorectal liver metastases that would otherwise require major hepatectomy was amended as an exclusion criterium, likely reducing the number of eligible candidates and potentially impacting outcomes in the control group. The Institutional Review Board and the Data Safety Monitoring Board supported the decision to prematurely terminate the trial, substantiated by the estimated residual trial duration, the increasingly difficult patient accrual and ethical concerns related to results from this analysis.

The results should be interpreted with a level of caution. Early cessation of accrual based on predefined stopping criteria makes it more difficult to draw definitive conclusions on the non-inferiority of thermal ablation regarding overall survival, specifically in the under-represented intermediate-disease and high-disease burden subgroups. Although the trial was halted to prioritise minimising harm and safeguarding participants, whether a subset of patients might have benefited more from surgical resection than thermal ablation remains unclear. The inclusion of patients with both few and many colorectal liver metastases, along with the allowance for some resections for non-ablatable colorectal liver metastases and vice versa for ablations of non-resectable colorectal liver metastases, might have influenced outcomes in some subgroups, potentially obscured by the broad inclusion criteria. The study was not powered to assess differences in ablation approaches (percutaneous [57%], laparoscopic [7%], or open [37%]) or to assess differences between ablation alone and ablation plus resection (27 [18%] patients) in the ablation group, which could have influenced overall outcomes. In COLLISION, thermal ablation was compared with surgical resection in dedicated high-volume centres and the procedures were done by experienced operators. The results cannot be automatically generalised to centres with less experience and the study group foresees the necessity to set up large-scale implementation programmes. The effect on clinical practice is likely to be modest in centres that already ablate difficult to resect colorectal liver metastases, but might be more pronounced in those with previously limited adoption of thermal ablation. The outcomes should be evaluated alongside the recently published TRANSMET trial, which explored liver transplantation for patients with unresectable colorectal liver metastases, and future studies investigating the added value of adjuvant and neoadjuvant pump chemotherapy.[29,30] The results underscore the importance of collaboration and the need for an ablation expert to be present during multidisciplinary team meetings. Although the use of induction chemotherapy was evenly distributed across both treatment groups, it might have affected oncological outcomes, particularly in comparison with other geographical regions. The frequency of induction chemotherapy use aligns with the European Society for Medical Oncology guidelines, which recommends it selectively. According to these guidelines, induction chemotherapy for patients with upfront locally treatable disease is advised in specific cases where it might increase the chances of achieving technical success and for those at high risk of disease recurrence.[1]

To conclude, the assumption that thermal ablation should only be used for unresectable colorectal liver metastases needs to be reconsidered and our results advocate a more individualised approach to treatment, taking into account the specific clinical characteristics of each patient as well as the expertise available within the medical team.

Contributors

MM, RP, HS, and MPvdT were involved in the study design and funding acquisition. MD, RP, HHS, DV, ES, and SvdL oversaw the quality of the trial, and were responsible for data curation and project administration. RP, MD, and SvdL extracted the data, analysed the results, prepared the figures, did the literature search, and wrote the initial manuscript. MM, MD, and BLW have accessed and verified all the data underlying the manuscript. ES, HHS, DV, MD, RP, SvdL, HS, JdV, RJS, MPvdT, and MM were involved in the investigation. All authors contributed to the conceptualisation, data curation, drafting, and writing as well as review and editing of the manuscript, and approved the final version. All authors had direct access to underlying data reported in the study.

Data sharing

For eligible studies, qualified researchers can request access to individual, de-identified, patient-level clinical data through a data request. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the COLLISION collaborator group in terms of scientific merit and ethical considerations, including patients' consent. Data requests can be submitted to the corresponding author mr.meijerink@amsterdamumc.nl.

Declaration of interests

MRM declares funding related to the present manuscript from Medtronic Covidien; receipt of institutional grants from Medtronic Covidien, Angiodynamics, Johnson&Johnson, and Immunophotonics, outside the submitted work; consulting fees from Angiodynamics, outside the submitted work; payment for lectures and presentations from Medtronic Covidien, Johnson&Johnson, and Philips Medical, outside the submitted work; travel grants from Angiodynamics, outside the submitted work. SvdL declares receipt of an institutional grant from Medtronic Covidien; and payment for lectures and presentations and travel support from AngioDynamics, outside of the submitted work. RSP declares receipt of grant from Terumo, Sirtex, AngioDynamics, MML-Medical, Sectra, Dutch Society for Interventional Radiologie; consulting fees from Medtronic Covidien; payment for lecture from Medtronic Covidien and AngioDynamics; support for attending meetings from AngioDynamics; and leadership or fiduciary role in other board from Dutch Society of Interventional Radiology, outside of the submitted work. HJS declares consulting fees and payment for lectures and presentation from AngioDynamics; and support for attending meetings from CIRSE and Spectrum conference, outside of the submitted work. MCB declares receipt of institutional grant from Innovative Health Initiative–EU HORIZON and KWF (Dutch Cancer Society); payment for lectures and presentations from Philips and RIDN; participation on a DSMB for PLASTICS-3 and Dutch Liver Patient Organization Advisory Board; and leadership or fiduciary role in Dutch Benign Liver Tumor Group and Scientific Committee Dutch Society of Interventional Radiology, outside of the submitted work. CGO declares receipt of institutional grants from Siemens Healthineers, outside of the submitted work. MLJS declares payment for lectures and presentations from Medtronic Covidien, Teruma, and Philips to institution, outside of the submitted work; and Chair of Scientific Committee of Dutch Interventional Radiology Society (unpaid). CvdL declares receipt of institutional IHI Horizon Grant from IMAGIO wp3. BG declares receipt of institutional grant from AngioDynamics, Prins Bernhard Culuur Fonds, and Nijbakker Morra Stichting; and financial support for PhD thesis from AngioDynamics, outside of the submitted work. MB declares receipt of institutional grants from Intuitive, Medtronic Covidien, Oncosil and Ethicon, outside of the submitted work. JH declares payment for proctoring from Intuitive Surgical, outside of the submitted work. RJS declares payment for proctoring from Intuitive Surgical, outside of the submitted work. RMvD declares receipt of an institutional grant from KWF, ZonMw, National Institute for Health and Care Research, Canadian Institutes of Health Research, Abbot, and Guerbet, outside of the submitted work. TEB declares payment for lectures and presentations from Pierre Fabre; and advisory board BMS, outside of the submitted work. TC declares consulting fees from Cascination, outside of the submitted work. All other authors declared no competing interests.

Acknowledgments

We thank the funder of this trial, Medtronic-Covidien. We thank all patients and their relatives who participated in this study. We also thank the following persons for their help and advice during the conduct of the COLLISION trial: W Prevoo, interventional radiologist at UMC Utrecht, and CHC de Jong, hepatobiliary surgeon at Maastricht UMC. A comprehensive acknowledgement section is available in the appendix (p 4).

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