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STEREOTACTIC MICROWAVE ABLATION AS AN ALTERNATIVE TO SURGICAL RESECTION FOR COLORECTAL CANCER LIVER METASTASES

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Stereotactic Microwave Ablation as an Alternative to Surgical Resection for Colorectal Cancer Liver Metastases

Thesis for Doctoral Degree (Ph.D.)

By

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To

Pablo & Claire

Medicine is a science of uncertainty and an art of probability

Sir William Osler

Popular science summary of the thesis

Cancer of the large intestine (colon and rectum) represents the second most common type of cancer and second most common cause of cancer-related death worldwide. This has a relevant impact on the global burden of disease, affecting patients' illness and healthcare systems' costs significantly. Around a third of patients affected with cancer of the large intestine develop a spread of cancer cells from the intestine to the liver, which represents the most frequent cause of death in these patients. Over many years, surgery has been the gold-standard to treat these deposits of cancer cells in the liver (CRLM), leading to a significant increase in patients' survival when compared to no treatment or treatment with chemotherapy alone. More recently, other treatment modalities such as thermal ablation arose, destroying the CRLM locally with heat, while sparing a maximum of surrounding healthy liver tissue. This allows to treat CRLM repeatedly in case they reoccur in the future, which they do in 70% of patients, and to decrease the complications and time spent in-hospital when compared to treatment with surgery. Next to these advantages, thermal and specifically microwave ablation, was also shown to lead to similar survival outcomes as resection, but results from scientific studies comparing outcomes after ablation to resection in controlled studies following patients forward in time are not yet available. The aim of the studies included in this thesis was to create high-level evidence investigating if treatment with ablation potentially leads to patient survival similar to that after the gold-standard surgery, while decreasing treatment related complications, time spent in-hospital and healthcare related costs. The highest-level available precision technology for microwave ablation treatment was applied (SMWA), and in the data collected, the utility of a novel algorithm for evaluation of treatment success after SMWA was investigated.

In Study I, the probability of patients to survive 3 years after treatment with microwave ablation or surgery was studied by analysing data on all patients treated for CRLM in Sweden between 2013 and 2016. The two groups were rendered similar in terms of characteristics affecting both the choice of treatment (such as age, accompanying illness, fitness, and others) and patients' survival, by using statistical methods to account for these factors. Thereafter, survival 3 years after treatment was similar in both groups.

A further study was designed to study survival 3 years after treatment with SMWA, following patients forward in time, conducted at three European hospitals. Patients with small CRLM, who would have qualified for both treatments (surgery and SMWA), were deliberately treated with high-level precision technology SMWA. Survival in this study group was compared to survival in a group of patients who underwent surgery for similar types of CRLM, again after making the groups similar in terms of baseline characteristics **(Study IV).** Survival was similar in both groups, with significantly reduced treatment related complications and time spent in-hospital after SMWA. The subset of patients included in Sweden was analysed separately **(Study III)**, since a particular pattern of patient inclusion into the trial, only every other week, led to a methodological situation making the distribution of baseline characteristics between included patients (treated

with SMWA) and non-included patients (treated with the gold-standard surgery) more similar and thus treatment groups more "comparable". The total costs related to healthcare consumption, including the index treatment and two years onwards, were significantly lower in patients treated with SMWA compared to patients treated with surgery. CRLM returned and were re-treated more frequently in the MWA group, with however similar survival 2 years after SMWA or surgery. Complication rates and time spent in medical facilities were decreased after SMWA as opposed to surgery.

Study II investigated the utility of a novel algorithm for the precise calculation of ablation margins (the adequate appliance of heat energy with a sufficient margin to ensure complete destruction of all cancer cells), and therefore treatment success, with SMWA. The algorithm allows to calculate margin more precisely and quantifiably than previous techniques to evaluate ablation margins. Its potential to predict the occurrence of a return of cancer cells at the treatment site (and therefore failure to treat CRLM in a sustainable way) was investigated, and a significant effect of the size of ablation margins confirmed.

In conclusion, the results from the conducted studies underline the importance of thermal ablation, and specifically SMWA, as a valid treatment alternative to surgery for patients with small CRLM, leading to similar patient survival within 3 years after treatment. Preserving a maximum of healthy liver tissue, they allow easier re-treatments in case of cancer reoccurrence in the liver, and lead to lower complication rates, time spent in medical facilities and costs. These advantages gain increasing importance considering the overall ageing population, with often more severe accompanying illnesses and being more prone to complications when spending time as hospital inpatients. Findings from the current studies might aid physicians in future decision-making processes towards designing optimal and personalised patient care.

Abstract

Colorectal cancer (CRC) implies a substantial global burden of disease with a relevant impact on the general population and on healthcare systems in terms of morbidity, mortality, quality of life, and costs. A raising CRC incidence emphasises the need to refine screening and prevention strategies, and design optimal algorithms for treatment indication and outcome prediction. Around 25% to 30% of patients with CRC develop colorectal cancer liver metastases (CRLM) at any time point during their disease, with high variation in the disease presentation, severity, chronology and response to treatment. This and the increasing quantity and quality of available therapeutic options, enhance the complexity of defining treatment algorithms and designing feasible studies leading to meaningful results. Considering the high rate of tumour recurrence after initial CRLM treatment with curative intent, applying low-morbidity local treatments enhancing the possibilities of repeat treatments, are gaining importance. As such, thermal ablation (TA) promises high rates of local tumour control and favourable oncological outcomes comparable to the gold-standard surgical resection. Nevertheless, results from high-quality prospective comparative studies are missing, hampering the integration of TA as a valid treatment alternative into current guidelines. The aims of the studies included in this thesis were to investigate i) non-inferiority in overall survival (OS), and compare healthcare consumption, costs and treatment-associated morbidity, when treating patients with *potentially resectable* CRLM with TA versus resection, while applying high-level navigation technology for stereotactic microwave ablation (SMWA), and ii) the potential of a novel algorithm for computation of 3D quantitative ablation margins (QAM) to enhance treatment success and predict local tumour control after SMWA.

Study I was a population-based analysis comparing 3-year OS after microwave ablation (MWA) versus resection using data from a nationwide Swedish patient registry. After adjusting for factors known to affect the treatment type and OS (confounding by indication) using propensity score (PS) analysis, 3-year OS probabilities were similar in patients treated with MWA (n = 70) (76%, CI 59% to 86%) versus resection (n = 201) (3-year OS 76%, CI 68% to 83%), with a change in the hazard of death of 1.43 (CI 0.77 to 2.65) induced by the treatment type in a multivariable model.

Studies II, III and IV were analyses or sub-analyses of a prospective, multi-centre cohort study (MAVERRIC study), comparing patients with ≤ 5 CRLM ≤ 3cm in size, qualifying for both SMWA *and* resection and deliberately treated with SMWA *(study group),* to a contemporary cohort of patients treated with resection, extracted from a Swedish nationwide patient registry *(control group).* The primary outcome of 3-year OS after a prospective follow-up of 3 years was analysed in **Study IV**. PS analyses yielded comparable groups with a balanced distribution of baseline characteristics across the study (n = 98) and control (n = 158) cohorts. Three-year OS was non-inferior after SMWA (78%, CI 68% to 85%) versus resection (76% (CI 69% to 82%), with a hazard ratio (HR) of 1.09 (CI 0.69 to 1.51) for the treatment type (SMWA over resection).

In the Swedish subgroup of patients included into the MAVERRIC study, a particular inclusion pattern (patients amenable to both ablation and resection treated with SMWA every *even* week and with resection every *odd* week) created a quasi-randomised situation**,** where healthcare related costs and OS were analysed **(Study III)**. Overall costs (all inpatient hospital admissions, outpatient visits, oncological treatments and radiological imaging) from the time of index treatment indication and two years onwards, were significantly reduced in the SMWA versus resection cohorts. Two-year OS and disease-free survival were similar, while hepatic recurrence-free survival was shorter and hepatic re-treatments more frequent after SMWA. Morbidity and length of hospital stay were significantly reduced, and re-treatment significantly more frequent, after MWA / SMWA versus resection, in Studies I, III and IV.

Study II was a secondary outcome-analysis applying a novel QAM metric on a subgroup of patients treated with SMWA within the MAVERRIC study. 3D-QAM was retrospectively computed to 65 CRLM treated with SMWA, and varying definitions investigated in a multivariable model. 3D-QAM was the most relevant factor affecting the occurrence of local recurrence within one year of treatment.

In conclusion, OS at 3 years may be considered similar after SMWA versus resection in patients with potentially resectable small CRLM, with significantly reduced morbidity, time spent in medical facilities and healthcare related costs. In an ageing and more comorbid population, this supports the role of TA as a valid low-morbidity, tissue-sparing treatment alternative, enhancing options for re-treatments in case of hepatic recurrences. This and the potential of innovative technology to enhance safety, efficacy and reproducibility of results, might aid decision-making when designing individualised treatment algorithms for patients with CRLM.

List of scientific papers

I. **Microwave ablation versus resection for colorectal cancer liver metastases - A propensity score analysis from a population-based nationwide registry**
Pascale Tinguely, Gabriella Dal, Matteo Bottai, Henrik Nilsson, Jacob Freedman, Jennie Engstrand
European Journal of Surgical Oncology, 2020;46(3): 476-485. doi: 10.1016/j.ejso.2019.12.002

II. **3D Quantitative Ablation Margins for Prediction of Ablation Site Recurrence After Stereotactic Image-Guided Microwave Ablation of Colorectal Liver Metastases: A Multicenter Study**
Simeon J. S. Ruiter / Pascale Tinguely (shared first authorship), Iwan Paolucci, Jennie Engstrand, Daniel Candinas, Stefan Weber, Robbert J. de Haas, Koert P. de Jong, Jacob Freedman
Frontiers in Oncology, 2021 Nov 15;11:757167. doi: 10.3389/fonc.2021.757167

III. **Ablation versus resection for resectable colorectal liver metastases - Health care related cost and survival analyses from a quasi-randomised study**
Pascale Tinguely, Gustaf Laurell, Anton Enander, Jennie Engstrand, Jacob Freedman
European Journal of Surgical Oncology, 2023 Feb;49(2):416-425. doi: 10.1016/j.ejso.2022.09.006

IV. **Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases (MAVERRIC): A prospective multi-center propensity score matched cohort study**
Pascale Tinguely, Simeon Ruiter, Jennie Engstrand, Daniel Candinas, Robbert J. de Haas, Henrik Nilsson, Koert P. de Jong, Jacob Freedman
European Journal of Cancer, 2023 Apr 5;187:65-76. doi: 10.1016/j.ejca.2023.03.038

Scientific papers not included in the thesis

A. **Volumetric Quantitative Ablation Margins for Assessment of Ablation Completeness in Thermal Ablation of Liver Tumors**
Raluca-Maria Sandu, Iwan Paolucci, Simeon J. S. Ruiter, Raphael Sznitman, Koert P. de Jong, Jacob Freedman, Stefan Weber, Pascale Tinguely
Frontiers in Oncology, 2021 Mar 10;11:623098. doi: 10.3389/fonc.2021.623098

B. **Stereotactic and Robotic Minimally Invasive Thermal Ablation of Malignant Liver Tumors: A Systematic Review and Meta-Analysis**
Pascale Tinguely, Iwan Paolucci, Simeon J. S. Ruiter, Stefan Weber, Koert P. de Jong, Daniel Candinas, Jacob Freedman, Jennie Engstrand
Frontiers in Oncology, 2021 Sept 23;11:713685. doi: 10.3389/fonc.2021.713685

C. **Volumetric analyses of ablation dimensions in microwave ablation for colorectal liver metastases**
Iwan Paolucci, Simeon J. S. Ruiter, Jacob Freedman, Daniel Candinas, Koert P. de Jong, Stefan Weber, Pascale Tinguely
International Journal of Hyperthermia, 2022;39(1):639-648. doi: 10.1080/02656736.2021.1965224

Contents

List of abbreviations

5-FU	5-Fluorouracil
AJCC	American Joint Committee on Cancer
ALPPS	Associating liver partition and portal vein ligation for staged hepatectomy
AI	Artificial intelligence
ASCO	American Society of Clinical Oncology
ASA	American Society of Anaesthesiology
ASR	Age-standardised rate
AUC	Area under the ROC curve
AVI	Ablation volume irregularity
BRAF	B-Raf proto-oncogene
CAPOX	Capecitabine-oxaliplatin
CCI	Charlson comorbidity index
CE	Contrast-enhanced
CEUS	Contrast-enhanced ultrasound
CI	Confidence interval
CRC	Colorectal cancer
CRLM	Colorectal cancer liver metastases
CRS	Clinical risk score
CT	Computed tomography
DEBIRI	Drug-eluting bead with irinotecan
DHGP	Desmoplastic histological growth pattern
DFS	Disease-free survival
DLM	Disappearing liver metastases
EAV	Effective ablation volume
ECOG PS	Eastern Cooperative Oncology Group Performance status
EGFR	Epidermal growth factor receptor
EM	Electromagnetic
ESMO	European Society for Medical Oncology

FDG-PET	Fluorine-18-fluorodeoxyglucose positron emission tomography
FLR	Future liver remnant
FOLFOX	5-FU-leucovorin-oxaliplation
GAME	Genetic And Morphological Evaluation
GEE	Generalised estimating equation
HIFU	High-intensity focused ultrasound
HPB	Hepato-pancreato-biliary
HGP	Histological growth pattern
HIPEC	Hyperthermic intra-peritoneal chemotherapy
HR	Hazard ratio
IOUS	Intraoperative ultrasound
IR	Interventional radiology
IRE	Irreversible electroporation
KRAS	Kirsten rat sarcoma oncogene
LOS	Length of hospital stay
LR	Local recurrence
MAM	Minimal ablation margin
MAVERRIC	Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases
MDT	Multi-disciplinary team
MI	Minimally-invasive
MMR/MSI	Mismatch repair / Microsatellite instability
MRI	Magnetic resonance imaging
MWA	Microwave ablation
NED	No evidence of disease
NICE	National Institute of Health and Care Excellence
OMD	Oligometastatic disease
OS	Overall survival
PS	Propensity score

QALY	Quality-adjusted life years
QAM	Quantitative ablation margin
QOL	Quality of life
RCT	Randomised controlled trial
ROC	Receiver operating curve
RFA	Radiofrequency ablation
SIRT	Selective internal radiation therapy
StD	Standardised difference
RFS	Recurrence-free survival
SBRT	Stereotactic body radiation therapy
SMWA	Stereotactic microwave ablation
TA	Thermal ablation
TARE	Transarterial radioembolisation
TBS	Tumour Burden Score
UICC	Union for International Cancer Control
US	Ultrasound
VEGF	Vascular endothelial growth factor

1 Introduction

1.1 Colorectal cancer

1.1.1 Epidemiology

Colorectal cancer (CRC) is the second most common cancer in both males and females (5-year prevalence 5'253'335 cases, 10.4% of all cancer cases), the third most frequently newly diagnosed cancer (incidence 1'931'590 cases, 10% of all cancer cases) and the second most common cause for cancer-related death (mortality 935'173 cases, 9.4% of all cancer cases), for all ages, worldwide, in 2020[1].

A wide variation in the incidence of CRC exists between sex, race and geographical regions (Figure 1), with highest rates in high to very high-income countries, among males and in the Afro-American and American-Indian populations[2]. In Europe, the age-standardised incidence rate (ASR) of CRC is 30.4 per annum per 100'000, with a lower incidence rate in women (24.6) than men (37.9)[1].

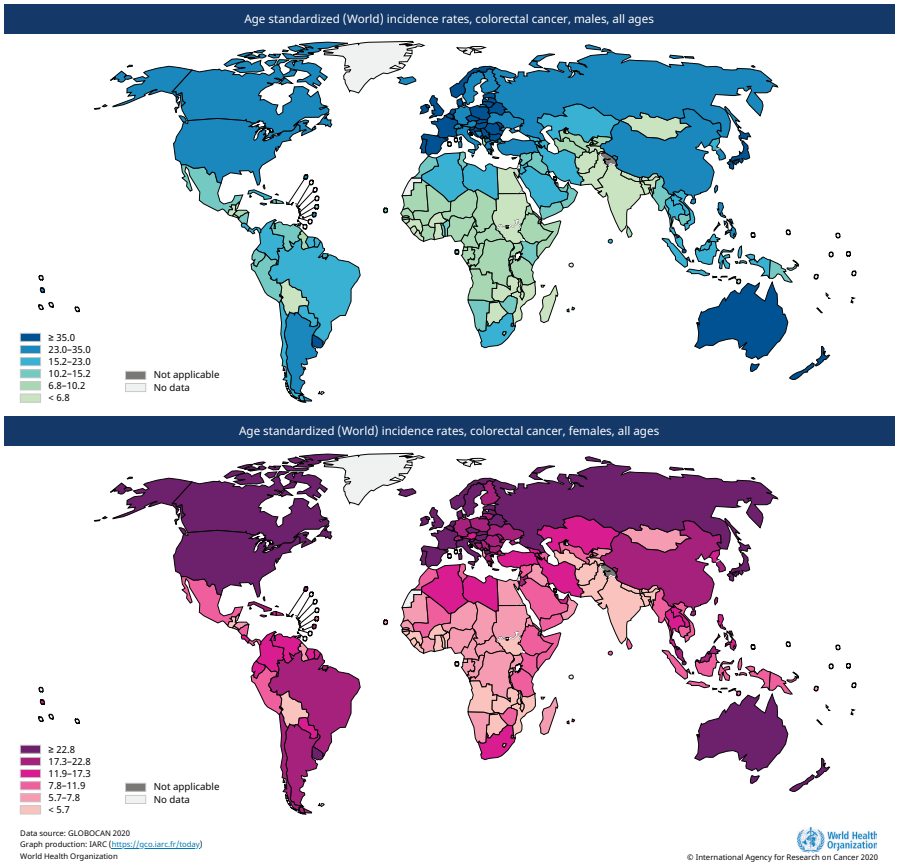

Figure 1. Age standardised incidence rates (ASR World) for colorectal cancer, per 100'000, in 2020, for males (top) and females (bottom). Extracted from: The Global Cancer Observatory: Cancer Today. Reprinted with permission from[1]

Globally, the ASR for CRC incidence has increased from 1990 to 2019, however trends differ across regions and countries. While incidence rates have been increasing in several Eastern and Southern European and Asian countries (e.g. Poland, Slovenia, India, Thailand), incidences are stable in most of Western Europe and steadily decreasing in the United states and Canada since the 1980ies[2,3]. The increase in CRC incidence in developing countries is attributed to a growing "Westernization" and adaption of lifestyle-related risk factors for CRC[4]. These include smoking, alcohol consumption, unhealthy diets (low intake in fruits and vegetables, high intake in red and processed meat), a sedentary behaviour, physical inactivity and obesity. Around 70 to 75% of CRC cases are associated with such modifiable risk factors and occur sporadically, whereas 25 to 30% of cases are linked to genetic factors, a positive family history, previous colonic polyps or adenoma or to hereditary syndromes (e.g. Lynch syndrome or familial adenomatous polyposis)[5]. A simultaneous increase in the access to screening programmes and raising life expectancy contribute to the growing incidence rates in these countries[4].

The stable and even decreasing incidence of CRC in countries with high socio-economic indexes are thought to partially be the effect of longstanding and effective screening programmes, which after the initial short-term growth, lead to a long-term reduction in CRC incidence[6,7]. Evolutions in the incidence patterns of CRC include shifts in the anatomical location of diagnosed CRC toward right-sided proximal colon and cecal cancers, which is higher with increasing age, in females and by year of diagnosis[8]. The reasons are thought to be partly due to an increased level of screening for distal CRC with greater likelihood of prior polypectomy and thus cancer prevention[9]. Other factors include hormonal effects and differences in genetic susceptibilities to carcinogens triggering varying pathogenetic mechanisms, since proximal and distal CRC arise from different embryologic origins[10]. A sedentary lifestyle has further shown to increase predominantly proximal CRC[11]. Furthermore, a trend towards an isolated increase in CRC incidence in the population of age 50 years and younger has further emerged in several high-income countries (e.g. the United States, Canada, Australia, United Kingdom, Sweden and Germany), predominantly in left-sided and rectal cancers, and in CRC diagnosed at later stages[12]. This is thought to be multifactorial and partly attributed to alterations in genetics, lifestyle and the gut microbiome[13].

Mortality rates have unanimously decreased over the last years in the "Western world"[2,3], resulting in improved age-specific 5-year survival rates of around 50 – 70% across all CRC stages[14]. This is attributable to improvements in diagnostic, strategic and therapeutic approaches to CRC treatment, improving overall disease prognosis[15]. In other countries with lower socio-economic indexes such as in Latin America and Asia, mortality rates are still increasing due to reduced or delayed access to healthcare allowing diagnosis and treatment of CRC disease[3]. Equally to sex disparities in CRC incidence, which are attributed to decreased prevalence of lifestyle-related risk factors and a protective effect from endogenous oestrogen and potentially oral contraceptives in women[16,17], the mortality from CRC is also lower in women[18]. This was partially explained by differences in molecular profiles such as MSI, and the influence of sex on the circadian effect of chemotherapy on survival in metastatic CRC[18,19].

Overall, the global burden of CRC is expected to increase by 68% to 3.2 million new cases and to 1.6 million cancer deaths by 2040, if rates remain the same as in 2020, based on continuous demographic growth and ageing of the population[20].

1.1.2 Classification and prognosis

Colorectal cancer is classified into four tumour stages, corresponding to different levels of disease severity at the time of CRC diagnosis. The most commonly used staging system is the TNM classification system developed by The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), currently available in its 8th edition[21]. It describes the tumour extent (T), extent of tumour spread to lymph nodes (N) and presence of distant metastases (M) (Table 1). Varying time points of acquiring this information are specified in the type of staging, including *clinical staging* (based on physical examination, imaging and biopsies), *pathological staging* (based on the examination of the surgical specimen together with clinical staging), *post-therapy* or *post-neoadjuvant therapy staging* and *recurrence* or *re-treatment staging*.

T category	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carinoma *in situ*, intramucosal carcinoma
T1	Invasion into submucosa
T2	Invasion into muscularis propria
T3	Invasion into pericolorectal tissue
T4a	Invasion into visceral peritoneum
T4b	Direct invasion/adherence to adjacent organs/structures
N category	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node involved
N1a	One regional lymph node involved
N1b	Two to three regional lymph nodes involved
N1c	Tumour deposits in the subserosa, mesentery on non-peritonealised pericolic or perirectal/mesorectal tissues
N2a	Four to six regional lymph nodes involved
N2b	Seven or more regional lymph nodes involved
M category	
M0	No evidence of distant metastasis
M1a	One site involved, without peritoneum
M1b	Two or more sites involved, without peritoneum
M1c	Peritoneum involved alone or with other organs

Stage	If T is..	If N is..	If M is..
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1, T2	N1	M0
	T1	N2a	M0
IIIB	T3, T4a	N1	M0
	T2, T3	N2a	M0
	T1, T2	N2b	M0
IIIC	T4a	N2a	M0
	T3, T4a	N2b	M0
	T4b	N1, N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Table 1. Classification of colorectal cancer according to The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC)[21]

The tumour stage, together with age at diagnosis, represent the most important prognostic factor in patients with CRC[21–23]. Overall survival rates vary considerably across tumour stages, with average 5-year OS rates of around 80% for stage I, 70% for stage II, 55% for stage III and 10% for stage IV CRC tumours, in analyses of population-based registry data from high-income countries[24].

Considerable geographical within-stage differences in survival exist across high-income countries, reflecting treatment disparities and the influence of other stage-independent factors[22]. These include the presence of bowel obstruction or perforation at time of diagnosis[25], surgical resection margins[26] and the presence of lymphovascular and perineural invasion in the CRC specimen, histologic tumour type and grade of tumour differentiation, the levels of Carinoembryonic antigen (CEA)[27], circulating tumour cells (CTC)[28], and molecular markers such as microsatellite instability (MMR/MSI), Kirsten rat sarcoma oncogene (KRAS) and B-Raf proto-oncogene (BRAF)[29]. A controversially discussed prognostic factor of overall survival (OS) is the location of the CRC tumour, with some studies reporting significantly longer cancer-specific patient survival for tumours located away from the caecum towards the sigmoid (rectum excluded)[30], and in right versus left-sided CRC[31]. However, other studies found no differences in stage-specific survival for right versus left-sided CRC, when analysis was adjusted for multiple patient, disease, comorbidity and treatment-related factors[27,32,33]. Others suggest that the tumour sidedness is a proxy to side-specific CRC mutational status and corresponding therapeutic response to targeted therapies[34], and that its value might decrease over the course of time in a patient's disease[35].

1.1.3 Treatment strategies

In parallel with the highly variable oncological behaviour, treatment strategies differ widely across CRC disease stages. They include surgical, pharmaceutical and radio-oncological approaches, and are managed by a multi-disciplinary team of gastroenterologists, surgeons, oncologists, pathologists, radiologists and radio-oncologists.

For hyperplastic or adenomatous polyps, non-invasive intraepithelial or intramucosal tumours and some invasive CRC tumours in the T1 stage, endoscopic resection with appropriate follow-up is sufficient. For other T1 tumours showing morphological (sessile or flat polyps) or histological (lymphatic or venous invasion, grade 3 differentiation, significant tumour budding) features associated with adverse outcome, the treatment of choice is surgical resection[36]. Equally, radical onco-surgical resection of the affected colonic/rectal area is the treatment of choice for most localised CRC (stage II and III), given the patient is a surgical candidate. This includes resection of an adequate intestinal segment, including its blood-supplying and draining vascular pedicle and the corresponding mesentery with optimally 12 or more lymph nodes[37], and *en-bloc* resection of infiltrated adjacent structures in case of T4b tumours[38]. In the setting of distant metastatic disease, resection of the CRC primary tumour is not recommended in patients with synchronous unresectable metastases, since no survival advantage was shown in randomised controlled trials (RCT)[39,40] - unless the patient is symptomatic with obstructive symptoms or bleeding from the CRC tumour.

Adjuvant chemotherapy is administered in most resected colon cancers to reduce tumour recurrence and prolong OS, after careful individualised examination of risks versus benefits[36]. The TNM stage remains the most relevant factor for risk assessment after colon cancer surgery, with 5-year OS rates after resection alone of 99% in stage I, 68% to 83%

in stage II and 45% to 65% in stage III disease[21]. While adjuvant therapy is indicated for all stage III colon cancers, a detailed evaluation of prognostic parameters is warranted for risk assessment in stage II colon cancers. These include a resected lymph node count of less than 12, pT4 stage including perforation, intestinal obstruction at presentation, perineural and lymphovascular involvement, poorly or undifferentiated tumour grades and elevated preoperative CEA levels[21,41,42]. Molecular markers with prognostic value such as MMR/MSI status further contribute to the decision-making in stage II disease, with e.g. MSI-high status leading to better recurrence-free survival (RFS) and OS[43]. While biomarkers such as postoperative circulating tumour DNA have shown some prognostic value regarding tumour recurrence[44], BRAF and KRAS mutations do currently not contribute to decision-making in non-metastatic disease[36]. Overall, adjuvant chemotherapy is reported to decrease the risk of death by 3% to 5% in high-risk stage II disease with single-agent 5-fluorouracil (5-FU) and by 10% to 15% in stage III disease with fluoropyrimidines (intravenous 5-FU plus Leucovorin or oral capecitabine (Xeloda®)), with an additional 4% to 5% decrease when adding oxaliplatin[36]. Increased disease-free survival (DFS) when adding oxaliplatin was further shown in three landmark trials (MOSAIC, NSABP C-07 and XELOXA trials[45–47]). The standard adjuvant chemotherapy regimen for stage III and intermediate and high-risk stage II colon cancer is therefore 5-FU-leucovorin-oxaliplation (FOLFOX) or capecitabine-oxaliplatin (CAPOX), for a duration of 6 months and 3 to 6 months, respectively[48].

For rectal cancers, therapeutic strategies include surgical resection by total mesorectal excision, with or without pre- or peri-operative radio- or chemo-radiotherapy, depending on the disease stage[49]. Similar to colon cancer, chemotherapy regimens for localised disease include fluoropyrimidines plus oxaliplatin, according to tumour stage and individual risk assessment, with targeted agents such as anti-epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) antibodies in case of metastatic disease.

1.2 Liver metastases from colorectal cancer

1.2.1 Epidemiology

Metastases from CRC arise via hematogenous, lymphatic, transperitoneal or direct dissemination. Because the venous drainage of the colon and upper part of the rectum occurs via the portal system, the primary site of distant metastasis is the liver (60% to 71%), followed by lungs (25% to 40%), peritoneum and distant lymph nodes, and less frequently bones (5% to 10%), ovaries (3% to 5%), adrenal glands (1%), the central nervous system (1%) and other sites[50]. Tumours in the lower part of the rectum may spread directly to the lungs via the inferior rectal vein and inferior vena cava. Approximately 20% to 25% of patients diagnosed with CRC already present with metastases (at any site) at the time of diagnosis (i.e. stage IV)[51], and another 20% to 50% will develop distant metastases at any site over the course of the disease[36].

The overall incidence of colorectal cancer liver metastases (CRLM) ranges between 15 to 37% in large population-based analyses[52,53], and represent the main cause of death in patients with CRC. At the time of CRC diagnosis, 15 to 25% of patients are diagnosed with CRLM (*synchronous* CRLM), with a wide range of reported liver-only metastases (50 to 80 %)[53–55]. The cut-off used to define synchronous as opposed to metachronous CRLM is proposed to be the time point of CRC diagnosis or during resection of the primary CRC tumour[56]. In large population-based analyses, the incidence of synchronous CRLM were significantly associated with age, occurring more frequently in younger age groups, and more frequently in men than in women[54,55]. Incidence rates for synchronous CRLM were shown to remain relatively stable over the last decades[54,55].

Another approximately 15 to 30% of patients with initially localised CRC will develop CRLM over the later course of disease (*metachronous* CRLM)[52,53,57,58]. Of these, around 85% of CRLM are reported to be diagnosed within the first year, 94% within the first two years and 98% within three years after CRC diagnosis[57]. The overall cumulative incidence was reported to be 4%, 12% and 13 to 17% at 1, 3 and 5 years, respectively[54,55]. The strongest prognostic factor is the primary CRC stage, with a stage-specific 5-year cumulative risk of 4%, 13%, 23 to 30% and 46% for stage I, II III and IV tumours, in patients with initially curative-intent resection of the primary CRC tumour (with or without metastases)[54,55]. The more than 2-fold increase in metachronous CRLM between stage II and III is described to persist up to 5 years after initial CRC diagnosis[55]. Further relevant factors for metachronous CRLM incidence are male sex, gross macroscopic features, histologic grade and resection margin of the primary CRC tumour, age below 75 years and the period of diagnosis, with decreasing CRLM incidence over the last decades in France[54,55,59]. The site of the primary CRC (left versus right-sided tumours) was not associated with metachronous CRLM incidence in various population-based reports[53,55].

Conflicting results are reported concerning the influence of synchronous versus metachronous diagnosis on patient survival. No prognostic value was found for the time point of CRLM diagnosis with regard to DFS or OS, even in sub-group analyses of different definitions for synchronous versus metachronous disease, in a Swedish population-based study[56]. Contrarily, a recent French analysis reported net survival rates of 42% versus 50% at 1 year, and of 6% versus 13% at 5 years for synchronous versus metachronous CRLM, respectively. Survival differences remained significant after adjusting for age, sex and CRLM location, with a trend to increasing divergence over the last decades, due to a substantial improvement in outcomes for metachronous disease[55]. Similar trends were reported in a Finnish analysis, where patients with late (> 12 months after CRC diagnosis) versus early (at or within 12 months of CRC diagnosis) metachronous CRLM had better 5-year OS (66 versus 50%) and higher resectability rates (28 versus 17%), suggesting refined possibilities for outcome assessment when using this definition for CRLM appearance[53]. In the latter study, the known association of the primary CRC lymph node ratio with the development of CRLM and DFS[60] was stronger in patients with early versus late metachronous CRLM appearance.

1.2.2 Diagnosis

The diagnosis of CRLM is made by radiological imaging, in conjunction with histology-proven primary CRC tumour diagnosis, mainly during staging of the CRC primary tumour or during follow-up after treatment of initially localised disease. The preferred imaging modalities for detection of CRLM include computed tomography (CT), magnetic resonance imaging (MRI) and fluorine-18-fluorodeoxyglucose positron emission tomography (FDG PET). MRI is the preferred first-line imaging technique in patients with no previous therapy, especially prior to local therapies including resection and local ablative treatments[61]. The combination of diffusion-weighted and gadoxetic acid-enhanced MRI was shown to be the modality of choice in the detection of CRLM, and superior to either modality alone, with an overall sensitivity of 96% and of 90% for lesions < 10 mm[62]. Figure 2 illustrates a typical appearance of a CRLM on gadoxetic acid-enhanced and diffusion-weighted MRI. Importantly, the same imaging modality as for diagnosis should be used for assessment of response after CRLM treatment. FDG PET can be applied as a second-line modality in patients requiring further work-up, e.g. in patient with increased tumour markers without evidence of metastases, and for the detection of

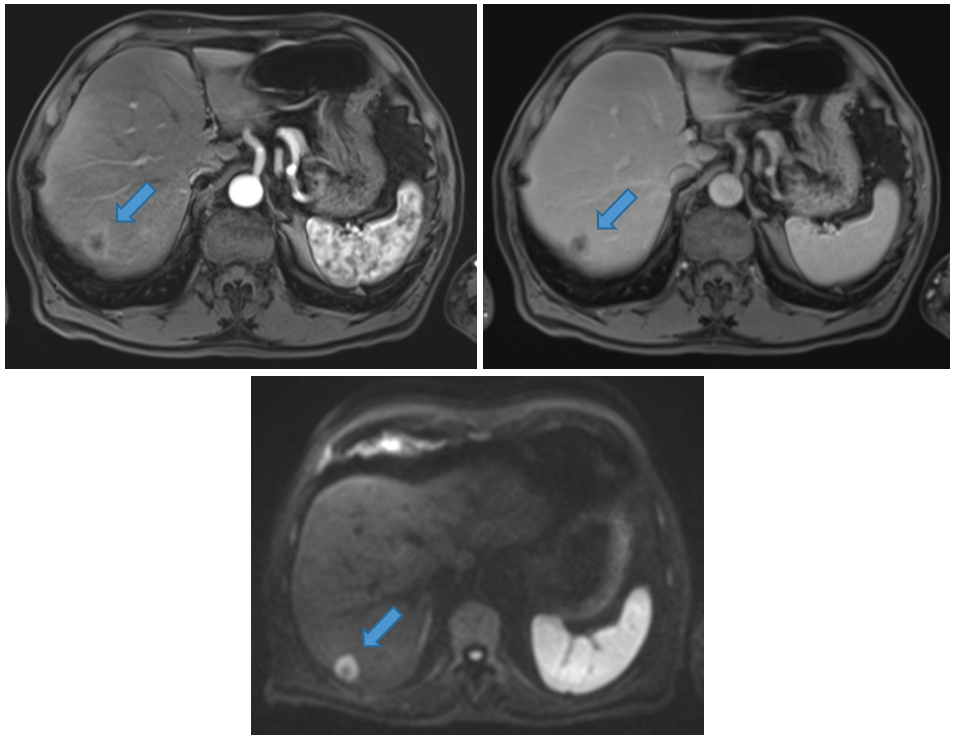

Figure 2. Typical appearance of a colorectal liver metastasis (blue arrow) in liver segment VIII on magnetic resonance imaging, with gadoxetic acid- rim enhancement on the early arterial phase (top left), washout on the delayed phase (top right), and high signal intensity on diffusion-weighted images (bottom)

extrahepatic disease[61]. Next to radiological imaging, a complete medical history and a physical examination, the primary work-up after CRLM diagnosis includes laboratory testing of the tumour markers CEA and optionally CA 19-9.

The testing of biomarkers and molecular targets, including MMR/MSI status, KRAS, BRAF and NRAS exon 2, 3 and 4 mutations, is recommended for all patients at the time of CRLM diagnosis, to adequately select chemotherapy regimens and targeted therapies[63,64]. Biopsies can be performed at any site, since a high concordance in biomarkers between the primary CRC tumour and metastases in the liver and lung were shown[65]. The analysis of MMR/MSI status supports decision-making regarding the use of immune check-point inhibitors and genetic counselling with regards to a potential Lynch syndrome. The analysis of KRAS mutational status is mandatory before initiation of treatment with anti-EGFR monoclonal antibodies, which are ineffective and contraindicated in KRAS-mutated disease (prevalent in around 44% of CRLM patients[66]). BRAF should be tested for its value as a negative prognostic factor, as well as its role for the choice of second- and third-line chemotherapeutic regimen[67]. If not already tested at diagnosis of the primary CRC tumour, dihydropyrimidine dehydrogenase deficiency should be assessed prior to initiating treatment with fluoropyrimidines[36].

1.2.3 Treatment strategies

Contrarily to most other cancers, there are significant differences in the prognosis within the metastatic stage IV CRC, depending on the biology and metastatic distribution pattern of the disease. After "curative-intent" resection of CRLM, long-term OS rates reach up to 74% (median around 40%) at 5 years and up to 69% (median 26%) at 10 years, with a median overall survival time reported between 3.6 to 5.2 years, as reported in different meta-analyses[68–70]. On the other end of the stage IV CRC distribution, chemotherapy can lead to prolonged survival of up to 40 months, but 5-year OS probabilities remain below 30%, even with newest chemotherapy agents[71–73]. These differences in prognosis have led to the sub-stratification of stage IV reflected in the latest 8th edition of the AJCC staging of colorectal cancer[21] (see Table 1). The wide range of reported OS rates reflect the significant disparities in the tumour biology and its clinical behaviour, and the heterogeneity in the patients' responsiveness to treatment, including a subgroup of patients showing no long-term survival benefit with treatment. This makes the standardisation of treatment algorithms for patients with CRLM challenging and requires careful risk stratification and individualised weighting of risks and benefits in each case. While available treatment decision-tools delineate pathways for groups of CRLM patients with similar presentation, current guidelines still suggest to include patients into clinical trials rather than following standard or accepted therapies[64].

The importance of discussing each patient's treatment approach in specialised multi-disciplinary team (MDT) meetings was shown, improving clinical outcomes in terms of resection rates and outcomes (DFS and OS)[74–76]. The core MDT representatives should include specialist physicians from medical oncology, pathology, diagnostic radiology, radiation oncology, colorectal and hepatobiliary surgery, gastroenterology and

stomatherapy[63]. With the increasing use of local interventional therapies, the presence of interventional radiologists and nuclear medicine specialists becomes indispensable. Despite standardised patient discussions at specialised MDT boards, large variations in practice patterns remain among centres and among medical specialists, specifically regarding the definition of *resectable* CRLM disease[77,78]. This highlights the importance of repeat MDT discussions, and re-definitions of treatment approaches throughout the course of a patient's disease[79], including a second reassessment of resectability after preferably 2 to 3 months of treatment in patients initially deemed unresectable[80].

1.2.3.1 Potentially resectable CRLM

The potentially high OS rates after CRLM resection have made liver resection the gold standard for treatment with *curative intent* in patients with resectable CRLM, as reflected in current guidelines (see chapter 2.3)[63]. At the time of CRLM diagnosis, around 10 to 30% of patients will have potentially resectable CRLM amenable to treatment with curative intent, depending on the tumour extent and distribution, and on the patient's medical conditions[52,57,68]. Another 10 to 30% will become resectable after induction chemotherapy[81–83]. Nevertheless, up to 75% of these patients will have recurrent disease over the course of their disease, warranting a cautious use of the word "curative". It remains frequently used to differentiate from a "palliative" situation where only systemic therapy is applicable, however, the definition of "cure" remains unclear. Some proposed a 10-year OS or RFS time, since recurrence is unusual after 10 years, others a DFS of 3 to 5 years[80,84]. Overall, improved surgical techniques and effective systemic regimens have increased the number of patients with CRLM that are considered technically resectable and thus defined amenable to curative-intent treatment[85].

Technical and oncological (prognostic) criteria define if a patient qualifies for surgical resection, and which perioperative chemotherapy regimen might aid improving long-term outcomes. The *technical* aspect of resectability is defined by the possibility of complete (R0) resection, preserving a sufficient functional liver remnant (FLR) (around 25 to 30% of the total liver volume in a healthy liver), with an adequate portal and arterial blood supply and sufficient venous and biliary drainage. Unfavourable technical criteria include e.g. vascular infiltration of the CRLM. *Oncological* criteria include prognostic factors such as onset of CRLM (synchronous versus metachronous), "clinical aggressiveness" such as short-term disease progression, multiple (> 3) and bilobar lesions or the presence of limited extrahepatic disease. Whether or not mutational status such as BRAF mutations should be considered in the initial decision-making is currently controversial[63]. Next to these technical and oncological criteria related to the CRLM, the patient's fitness for surgery and the accessibility of the abdominal cavity depending on the amount of previous abdominal surgery, affect a patient's CRLM resectability.

It was agreed that patients with favourable technical and excellent oncological criteria can be addressed with up-front surgery, since no added value of peri-operative chemotherapy in terms of OS has been shown[86]. Adjuvant treatment for 6 months can be administered, however, in the absence of high-quality evidence this cannot be

considered the standard of care. In case of technically resectable but unclear or less favourable oncological criteria, an initial round of systemic therapy can aid in gaining insight into the tumour's behaviour through the course of time. In this situation, a combination of leucovorin, 5-FU and oxaliplatin (FOLFOX), without molecular agents, for three months before and after surgery, is the standard of care[87,88]. Equally, in patients with CRLM of difficult technical resectability, a start with "best systemic therapy" will allow observation over the course of time and potentially lead to conversion into resectable disease. In this setting, the combination of a targeted agent (Anti-EGFR monoclonal antibody, e.g. Cetuximab, or Anti-VEGF agent, e.g. Bevacizumab) with a cytotoxic oxaliplatin-based doublet (FOLFOX) or triplet (FOLFOXIRI) is the standard of care[63]. Resection should be carried out as soon as CRLM become resectable, to avoid hepatic toxicity impacting peri-operative morbidity[51], and total peri-operative treatment should not exceed 6 months[63]. Contrarily, disease progression under systemic therapy is considered a poor prognostic factor, which should warrant re-consideration of treatments with curative intent. Figure 3 summarises the currently recommended pathways for patients with potentially resectable CRLM[63].

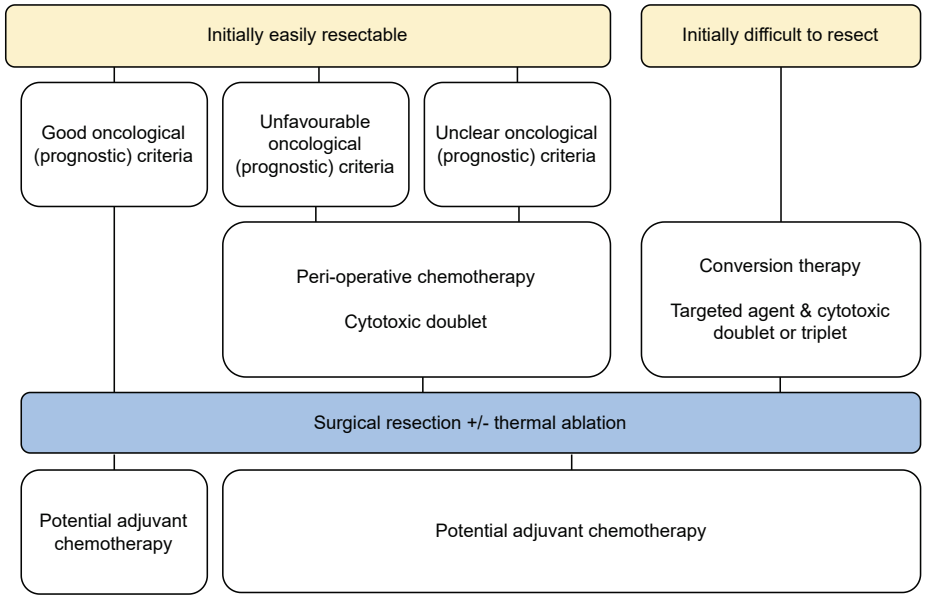

Figure 3. Treatment pathways for patients with potentially resectable CRLM according to the current guidelines of the European Society for Medical Oncology[63]

Pre-operative chemotherapy was not associated with increased postoperative morbidity and mortality in recent large propensity score (PS)-matched analyses, regardless of the treatment access[89,90]. However, recent meta-analyses have shown that the addition of peri-operative systemic chemotherapy for resectable CRLM can improve DFS, but not OS[91,92]. The response to neo-adjuvant chemotherapy is assessed radiologically, with a positive radiologic response described in around 65% of patients, usually indicating a

favourable tumour biology and prognostic outcome[93]. A *complete pathological* response after preoperative chemotherapy was described in 4% of resected CRLM patients, and in up to 30% in small CRLM ≤ 3cm, and was shown to be an independent predictor and potential surrogate parameter for OS[94]. Controversies exist regarding the management of CRLM with *complete radiological* response after systemic chemotherapy, resulting in disappearing liver metastases (DLM). The most accurate imaging modalities to assess DLM were shown to be MRI and contrast-enhanced intra-operative ultrasound (CE-IOUS)[95]. DLM are described to occur with an incidence up to 24%, with corresponding complete pathological response between 20% to 100% after resection and sustained clinical response (absence of LR) in up to 80%[96]. No consensus currently recommends surgical resection of DLM, however, the potentially high rates of persisting cancer cells in up to 80% suggest resection as the preferred strategy[97,98]. Meanwhile, a watch-and-wait strategy recently showed similar OS, but shorter DFS in patients with DLM[99,100].

In the case of synchronous CRLM, simultaneous resection of the CRC primary tumour and CRLM can be performed in selected patients with low surgical risk, leading to equal OS as in patients undergoing staged procedures[101–103]. The latter should be the preferred approach in patients at high surgical risk. Within staged procedures, the liver-first approach has gained popularity based on growing knowledge that the hepatic tumour burden drives the natural course of disease rather than the CRC primary tumour. A survival benefit was shown with the liver-first strategy when completion surgery of the primary CRC can be assured, which however failed in 25% of patients included in a recent meta-analysis, mainly due to interim hepatic progression[104]. Other analyses show similar short- and long-term outcomes when comparing the liver-first with traditional staged procedures of primary-first resection, followed by chemotherapy and CRLM resection[105].

1.2.3.2 Trends in CRLM surgery

Treatment paradigms have evolved from performing single-stage major hepatic resections toward using more multimodal, combined therapeutic approaches including parenchyma-sparing resection and minimally-invasive (MI) access techniques. This led to a higher rate of patients CRLM being considered resectable, especially also those with more extensive disease and multiple bilobar CRLM, and improved outcomes for these patients. Parenchyma-sparing resections include segmental and "atypical" local resection, where CRLM are resected with sufficient surgical margins, but not following traditional anatomical planes along segmental boarders. This decreases treatment-associated morbidity and improves the possibilities of hepatic re-treatments in the case of CRLM recurrence. Accordingly, average morbidity is reported between 30 to 45% for complex hepatectomies[106] and around 19 % for parenchyma-sparing resections[107]. A recent meta-analysis confirmed significantly improved perioperative outcomes with similar long-term RFS and OS with parenchyma-sparing surgery[108].

To further reduce treatment-associated morbidity, a MI treatment access such as a laparoscopic approach has become standard in many high-volume tertiary hepato-pancreato-biliary (HPB) centres[109]. Overall and major morbidity rates for laparoscopic liver

resections are aimed to be no more than 50% and 20% for major resections, and 11% and 0% for minor resections, in a recent benchmark study[110]. Similar morbidity rates were proposed in a study describing quality indicators for outcomes after liver surgery, specifying target rates for liver failure as < 8%, postoperative haemorrhage < 3%, biliary fistula < 10% and reoperation < 6%[111]. When compared to open resections, treatment-associated morbidity was significantly reduced after parenchyma-sparing laparoscopic resection in the OSLO-COMET RCT (19 versus 31%)[112], with similar long-term oncological outcome in terms of RFS and OS[113]. Recent meta-analyses confirmed improved short-term results and equal resection margins and long-term OS and DFS[114,115]. Another study even showed improved long-term outcomes when using a laparoscopic versus open approach[116]. Importantly, patient reported outcomes and health related quality of life (QOL) was shown to be enhanced when using a laparoscopic versus open approach for resection of CRLM[117]. Conversion rates of around 10% were reported for laparoscopic parenchyma-sparing resections in a recent meta-analysis[107], and both conversion rates and complications differ significantly between low-medium and large volume centres[109]. Regardless of the type of hepatic resection, postoperative complications are known to significantly affect long-term oncological outcomes in patients with CRLM[118–121], justifying all efforts to reduce treatment-associated morbidity.

Techniques to enhance resectability (Figure 4) in patients with more extensive disease, where traditional resection would lead to an insufficient FLR, include portal vein embolisation (PVE) and two-staged hepatectomy procedures. The latter consists in the first stage of CRLM "clearance" (resection with or without TA) in the liver lobe or segments to remain (FLR), combined with ligation or PVE of the portal branches supplying the contralateral liver parenchyma. Hypertrophy of the FLR and morbidity were shown to be similar after surgical portal vein ligation of percutaneous PVE[122]. In a second stage, after radiological assessment of sufficient growth in FLR volume, hepatectomy of the remaining CRLM is performed. In 30 to 40% of patients, PVE fails to induce adequate hypertrophy or early tumour progression precludes completion hepatectomy[123]. A technique of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was proposed in 2012[124]. The liver parenchyma is transected at the intended resection plane with clearance of CRLM in the FLR and simultaneous portal vein ligation in a first stage, before completing resection after liver hypertrophy in a second stage. A recent meta-analysis comparing two-staged procedures with ALPPS for patients with initially unresectable CRLM showed enhanced R0 resection and completion hepatectomy rates with however higher peri-operative morbidity for ALPPS, with similar risks of mortality, DFS and OS in both techniques[125]. More recently, complete venous deprivation with simultaneous embolisation of the hepatic vein additionally to the portal vein has been proposed to further enhance and accelerate hypertrophy of the FLR. A recent network meta-analysis confirmed the safety and efficacy of this technique, reporting significantly lower major morbidity and mortality with similar FLR hypertrophy as opposed to PVE and ALPPS[126]. A combination of surgical resection with TA has further been proposed to address multiple bilobar CRLM in a single procedure, avoiding dropout of patients after the first stage in two-stage hepatectomy. Results were promising with similar DFS and OS

and significantly lower morbidity associated with a combined strategy versus two-stage hepatectomy. In patients with CRLM deemed unresectable, a strategy of combined TA and resection was further shown to provide comparable OS rates as for patients with resectable CRLM treated with hepatectomy alone[127–129].

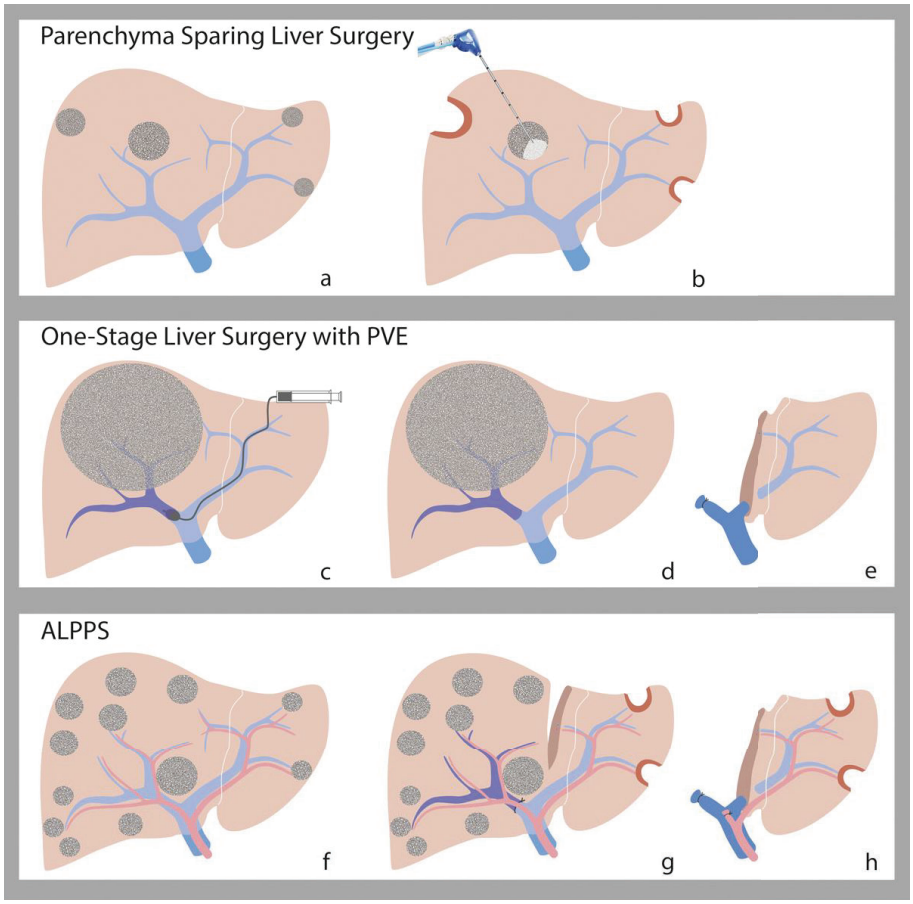

Figure 4. Techniques to enhance resectability by augmenting the future liver remnant. (a) Parenchyma with bilobar CRLM (b) After wedge resections of small peripheral CRLM and thermal ablation of a central lesion (c) One-stage liver surgery with portal vein embolisation on the lobe to be removed (d) Hypertrophy of the future liver remnant (e) Resection of the embolised liver lobe. (f) Bilobar CRLM before surgery (g) Open ligation on the right portal vein, cleaning of the future liver remnant and parechymal transition along the future resection line (h) Removal of the deportalised liver lobe. Reprinted with permission from[130] (non-adapted material, Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Public License, https://creativecommons.org/licenses/by-nc-sa/4.0/legalcode)

1.2.3.3 Local ablative treatments

Based on the experience that good prognosis can be achieved for selected patients with more extensive disease, emphasis has been put on a specific state called oligometastatic disease (OMD). This generally includes patients with a maximum of five CRC metastases limited to two metastatic sites, and with a controlled (optimally resected) primary CRC

tumour, and all metastases amenable to local treatments aiming to reach a status of "no evidence of disease" (NED)[63]. The concept of OMD has encouraged discussions toward a combination of modern systemic and local surgical and ablative therapies, to improve OS in these scenarios and widen the indication of a potentially curative treatment approach[131–136]. In an ageing population, a toolbox of locally effective but low-morbidity interventions may offer more aggressive treatment also to patients that previously would have been treated with palliative chemotherapy only (Figure 5). In most situations, there is no high-level evidence for selecting one modality over the other, and decisions should be made in MDT discussions considering also institutional availabilities and expertise and patient preferences[137].

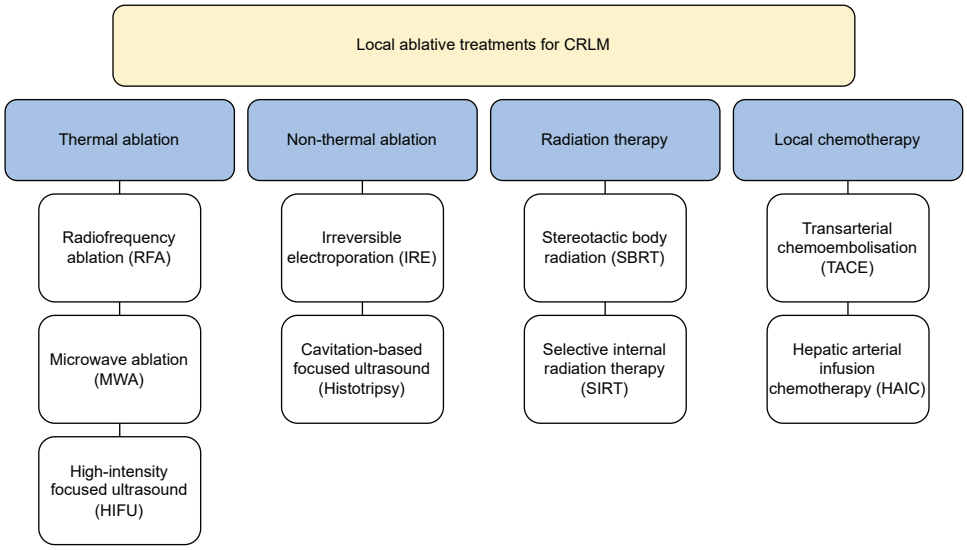

Figure 5. Toolbox of local ablative treatments for colorectal cancer liver metastases

The most frequently applied and reported local ablative treatment is TA, including radiofrequency ablation (RFA) and microwave ablation (MWA), where cancer cells are locally destroyed using thermal energy. The fundamental principles of TA and its use for CRLM specifically are elaborated in detail in chapters 1.3 and 2.1.

High-intensity focused ultrasound (HIFU) is a technique where ultrasound (US) energy of high power and high frequency is bundled to deliver a thermal effect (up to 80 °C) and locally destroy the targeted tumour tissue through coagulative necrosis[138]. First clinical applications for liver tumours showed an acceptable safety profile, with minor skin burns being the main treatment-related morbidity, and high precision in the creation of ablation volumes[139,140]. Two recent trials investigating HIFU for unresectable CRLM reported successful local control rates between 50 to 80%[141,142], and further clinical trials are needed to confirm the benefits of this treatment for CRLM. HIFU-based technological devices are also investigated for liver transection during hepatectomy (NCT02728167)[143].

Irreversible electroporation (IRE) is a non-thermal local ablation technique, where the delivery of high-voltage electric pulses via multiple parallel ablation antennas induce permanent disruption of cell membranes, which induces cell death via apoptosis[144]. IRE spares the extracellular matrix and as a result, preserves critical tubular structures poor in cells and rich in stromal tissue, such as blood vessels and bile ducts. IRE is thus thought to be a safe ablation technique for tumours adjacent to larger vascular and biliary structures, unlike thermal ablation where cell death is induced unselectively by coagulation necrosis[145]. IRE for CRLM has been proposed mainly for lesions not amenable to resection or TA due to their size or intrahepatic location, e.g as a salvage treatment for recurrence after major hepatectomy. A recent series of 23 patients showed a complete ablation rate in such situations in 96%[146]. Results from the prospective phase II COLFIRE-2 trial showed no differences in local recurrences (LR) for small and intermediate (3 to 5 cm) sized lesions, suggesting that this technique might be less susceptible to tumour size than other local ablation techniques[147]. Overall, few studies are available and little is known about the true benefit in patients with CRLM, and IRE for CRLM is thus not widely adopted[148]. Figure 6 illustrates a clinical case of a patient treated with stereotactic percutaneous IRE for a recurrent CRLM, not amenable to resection or TA, but with favourable tumour biology proven by a long (more than 10 years) disease-free interval between prior major hepatic surgery and CRLM recurrence.

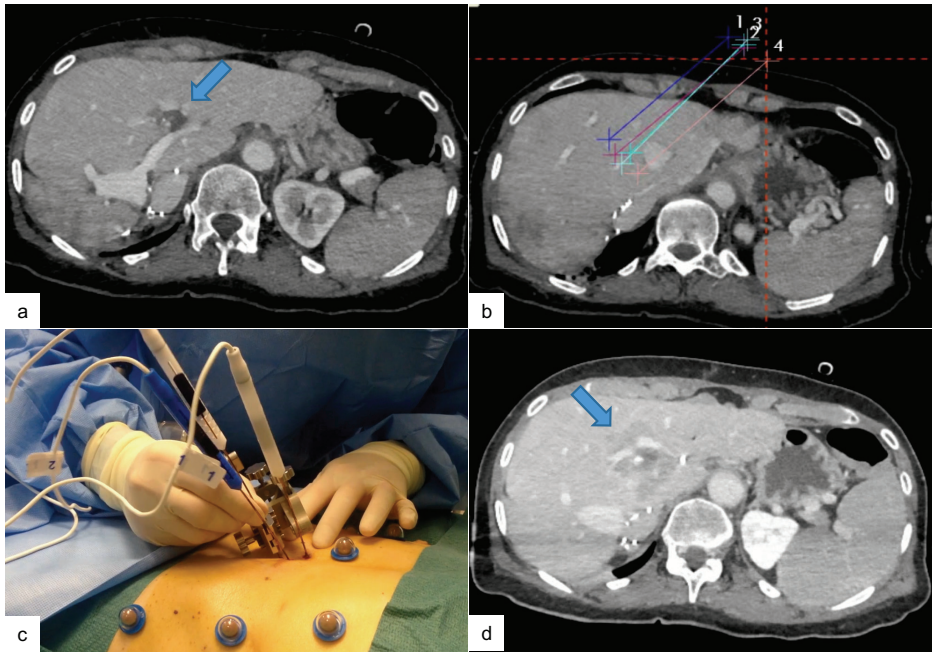

Figure 6. Clinical case of patient with a recurrence of colorectal cancer liver metastasis, not amenable to repeat resection or thermal ablation therapy, treated with stereotactic irreversible electroporation (IRE). (a) Colorectal liver metastasis (blue arrow) located between the main left portal vein branch and the only remaining hepatic vein after prior major liver surgery (b) Planning of IRE antennas around tumour (c) Stereotactic insertion of four IRE antennas (d) Post-ablation verification scan with ablated area (blue arrow) surrounding the ablated tumour and clearly preserved left hepatic vein branches

Cavitation-based focused ultrasound (histotripsy) is a non-thermal technique that uses US energy of high power and low frequency as a mechanical bioeffect to liquefy tissue into acellular debris[149]. As opposed to traditional HIFU, the low frequency leads to a mechanical effect as the major mechanism, enabling highly localised tissue disintegration without thermal damage to surrounding structures[150]. A further advantage is the lacking need of the insertion of an ablation antenna, reducing invasiveness to a minimum. *In-vivo* evaluations of histotripsy of the liver have shown promising results[151,152], and a first-in-man trial showed acceptable treatment success and safety in 8 patients[153]. The protocol of a European prospective trial (NCT04573881) has recently been published, investigating safety and efficacy of histotripsy for primary and secondary liver cancers[149].

Stereotactic body radiation therapy (SBRT) has been increasingly applied as a local treatment for unresectable CRLM, with potentially high local control rates of up to 90% after 2 years, with low morbidity and toxicity[154]. SBRT consists of the accurate delivery of a high radiation dose in a small number of fractions, which, next to the destruction of cancer cells, also damages adjacent stromal tissue inducing particular anti-cancer immune responses[155,156]. Important factors contributing to success of SBRT treatment are the administration of the adequate biologically effective tumour size-adapted dose, and successful motion control. While results are promising, data from large prospective studies are lacking, and it thus remains unclear which patients benefit most from this treatment modality. Ongoing RCT compare SBRT to MWA (NCT02820194) and to chemotherapy alone (NCT03296839) for patients with inoperable CRLM[63].

Another radiation-based technique is selective internal radiation therapy (SIRT), where radionuclides (typically Yttrium-90) attached to particles or microspheres are delivered trans-arterially. An improvement of liver-specific but not overall progression at any site was reported, and no improvement in OS was shown when adding SIRT to first-line chemotherapy in patients with unresectable CRLM in two phase III trials[157,158].

Transarterial chemoembolisation (TACE) is a combination therapy where drug-eluting particles are locally injected via the hepatic artery, delivering chemotherapeutic agents and abolishing the tumour's local blood supply. While this therapy is well established for primary hepatic tumours, the experience of TACE for CRLM treatment is much smaller and reported results are controversial. A Chinese retrospective propensity-score matched study showed no benefit in OS after TACE versus no TACE for unresectable CRLM, however, important information on prior chemotherapy was lacking in this study[159]. Contrarily, two RCT's reported a significant improvement in OS, progression-free survival and quality of life (QOL) after drug-eluting bead with irinotecan (DEBIRI) as opposed to systemic 5-FU-Leucovorine-irinotecan (FOLFIRI) for unresectable CRLM[160], and in response rate and progression-free survival after FOLFOX-bevacizumab-DEBIRI versus systemic FOLFOX-bevacizumab[161]. A recent systematic review confirmed improved rates of progression-free and OS with DEBIRI over system therapy[162]. DEBIRI was further shown to be equally effective as systemic chemotherapy in the neoadjuvant setting, with similar pathologic response and OS rates[163].

For hepatic artery infusion chemotherapy (HAIC), a port or pump is placed in the hepatic artery, surgically or via a percutaneous access, and chemotherapy (mostly floxuridine or oxaliplatin) infused locally. HAIC with oxaliplatin showed a significant increase in complete pathological response and associated longer OS and DFS as opposed to systemic therapy for patients with unresectable CRLM[164], and was shown to be safe[165]. A recent meta-analyses with 18 included studies confirmed improved OS after adjuvant HAIC for resected CRLM, which was most pronounced when using floxuridine, a surgical catheter insertion with a subcutaneous pump and concomitant systemic chemotherapy[166]. Conversion to resectable disease was reported in 30% with 5-FU-irinotecan-oxaliplatin-HAIC combined with systemic cetuximab[167], and in 47% with floxuridine-dexamethasone-HAIC and systemic oxaliplatin-irinotecan[168], highlighting its potential role in patients unresponsive to first-line chemotherapy[63].

1.2.3.4 Treatment of recurrent disease

Between 64% and 85% of patients develop new intrahepatic recurrences after local treatment of CRLM, regardless of the type of initial treatment (resection or TA)[120,132,169]. Median time to recurrence (RFS) after CRLM resection was 1.3 years (95% CI 1.3 to 1.4 years), with 85% of CRLM patient mortalities being preceded by recurrence, and a median time from recurrence to death of 2.0 years (IQR 1.0 to 3.4 years), in a recent meta-analysis[70]. Recurrences are confined to the liver in approximately 40%, and include the liver and other metastatic sites in 20%[170]. OS rates over 50% have been shown after repeat hepatectomy, justifying repeat and aggressive local re-treatments for recurrent CRLM[132]. Meanwhile, the role of induction chemotherapy prior repeat local treatment of recurrent CRLM remains unclear[171]. Depending on the extent of initial resection, remaining liver volume and on potential intra-abdominal adhesions, repeat resection can be challenging and associated with enhanced morbidity. In case of multiple chemotherapy regimens over the course of the disease, chemotherapy-associated liver injury including steatohepatitis and sinusoidal dilatation can lead to increased perioperative morbidity in case of repeat resection[172]. TA has therefore been proposed as the more attractive option in this scenario, with similar OS but favourable morbidity rates and length of hospital stay (LOS) as opposed to repeat resection[173–175]. A shorter RFS after repeat TA was shown in one of the analyses, not affecting OS[176]. In general, conflicting results are reported regarding the association of disease recurrence with long-term OS of patients after CRLM resection. While some studies describe DFS as a prognostic factor for OS[177], a recent meta-analysis found a minimal correlation, suggesting that RFS is an inadequate surrogate endpoint for OS in the treatment of CRLM[70]. Overall, the pattern of recurrence and timings of retreatments seem to be of greater importance[170,178], however, the crucial issue of *immortal time bias* limits internal validity of these reports (see also chapter 2.1).

1.2.3.5 Extrahepatic disease

While the presence of extrahepatic metastatic disease has long been seen as a contraindication for treatment of CRC with curative intent, growing evidence supports the use of local treatment of CRLM and concurrent extrahepatic metastases in well selected

patients with OMD[179–181]. In patients with lung-only metastases, the prognosis after resection appears to be similar as for patients resected for CRLM, with 5-year OS rates of 25 to 45%[182]. Equally, 5 and 10-year OS rates around 50% and 18% were reported for selected patients undergoing resection of synchronous CRLM and lung metastases[182,183]. A history of liver metastases was shown to be a negative prognostic factor in patients undergoing resection or TA for lung metastases[184,185]. Image-guided TA of lung metastases has shown equally high local control rates of up to 80% at 5 years[186–188]. Generally, the prognosis of patients with metastases confined to the liver and lung is improved as opposed to other metastatic disease locations[180]. Others suggest that the number of CRLM might be of greater importance than the site of extrahepatic disease[179].

In some CRC patients with very limited spread to the peritoneum, complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) might lead to an improved prognosis, however this was only shown for experienced high-volume centres[189] and was not reproduced in a recent trial[190]. Due to the potentially higher associated morbidity, HIPEC is therefore currently not yet recommended outside of clinical trials[63].

1.2.3.6 Unresectable CRLM without potential conversion

As for patients with potentially resectable CRLM, treatment decisions for patients with unresectable CRLM are based on the consideration of several factors, including the clinical presentation (tumour burden and location of both CRLM and CRC, symptoms at presentation), patients characteristics (age, comorbidities, performance score, expectations and preferences, compliance), the tumour's biology and molecular profile, and treatment-related issues (toxicity profiles, tolerances, QOL)[63]. Age alone is not a contraindication for combined treatment strategies, and the patient's fitness and comorbidity as well as a complete geriatric assessment will guide treatment decisions in older patients[191]. In patients with metastatic CRC not amenable to conversion therapy, the primary treatment goals consists of improving tumour-related symptoms, delaying progression and prolonging patient survival while maintaining QOL. In this group of patients, a concept of *continuum of care,* sequencing available therapeutic modalities, results in prolonged disease control and patient survival[192].

In most cases, first-line therapy of patients with unresectable metastatic CRC usually consists of a cytotoxic doublet (FOLFOX, FOLFIRI or CAPOX) combined with a biological agent (anti-VEGF or anti-EGFR monoclonal antibody), unless contraindicated. Patients with right-sided RAS-wild type primary CRC tumours (proximal to the splenic flexure) have a worse prognosis, related partly but not exclusively to a lesser benefit from treatment with anti-EGFR monoclonal antibodies, than patients with left-sided tumours[193]. Equally to RAS- and BRAF-mutated tumours, bevacizumab can be added to chemotherapy in these patients. Immune-checkpoint inhibitors such as pembrolizumab are added to standard chemotherapy in MMR/MSI-high patients. The current ESMO-guidelines summarise the first, second and third-line chemotherapy regimen concisely[63].

Liver transplantation (LT) has been evaluated for highly selected patients with non-resectable CRLM with liver-only metastases, and a survival benefit over palliative chemotherapy was suggested (5-year OS 60%)[194]. The *Oslo score* has been developed to aid patient selection, which considers the CRLM maximum tumour diameter, pretransplant CEA levels, the response to chemotherapy and the diagnosis-to-LT time interval[195–198]. With more stringent selection criteria, 5-year OS rates as high as 80% after LT have recently been reported, even comparing LT to surgical resection for patients with a high Tumour Burden Score (TBS)[199,200]. Ethical considerations must cautiously be considered in light of the overall limited organ availability, and weighted against competing indications for LT.

1.2.4 Prognostic factors

Due to the disease heterogeneity and large variations in individual treatment response, the summary and risk stratification of prognostic factors in CRLM disease is complex. Factors frequently described to significantly influence OS after resection of CRLM in multivariable or meta-analyses are clinical (Eastern Cooperative Oncology Group performance status (ECOG-PS) adapted by the WHO, sarcopenia[201,202]) and preoperative laboratory (CEA levels[68,203], neutrophil-to-lymphocyte ratio[204], circulating tumour cells[205–210]) parameters, pathological primary CRC tumour-related (T and N stage[68], left versus right-sided location[211], tumour grade[68], resection margins[68,203]) and CRLM-related (number and size[68,209]) factors, and molecular markers (RAS and BRAF mutational status[212,213]).

Both OS and DFS after CRLM resection were shown to be affected by the primary tumour CRC location, with tumours proximal to the splenic flexure (right-sided tumours) having a worse prognosis than left-sided CRC. Reasons are multiple, and include differences in embryological origin, patterns of molecular expression (more often MMR/MSI-High and KRAS and BRAF mutated) and histological properties (more often mucinous and associated with an inflammatory response)[193,214–216]. However, prognostic value of CRC sidedness was also shown independently from RAS mutational status[211]. Conflicting results have further been reported regarding the influence of the histopathological resection margin after CRLM surgery. While former analyses showed the R-status to be a significant independent prognostic factor for OS[217,218], others showed no influence of positive margins on patient OS,[219] especially when R1 occurs at the vascular pedicle[220]. More recently, the histological growth pattern (HGP) of resected CRLM was shown to be an independent predictor of OS[221,222]. The HGP describes the microarchitecture of CRLM and interactions of cancer cells with the hepatic microenvironment, where the desmoplastic HGP (DHGP) with a fibrous rim containing multiple immune cells separating cancer and liver cells is associated with significantly better outcome than non-DHGP lesions[223,224]. The HGP was further shown to be altered by pre-operative chemotherapy[225] and to have a potential direct impact on surgical resection margins[226]. An association between circulating tumour cells and preoperative detection of HGP was also reported[227]. Lastly, a multitude of other biomarkers and factors related to the host immune system interacting with tumour biology, treatment response and disease prognosis have been described, highlighting the

importance of algorithms investigating complex interactions of predictive factors towards multidisciplinary tailored treatment approaches for CRLM patients[66,134,228].

Several clinical risk scores (CRS) have been developed, aiming to predict tumour recurrence after surgical resection of CRLM and thus aid decision-making regarding the indication for surgery. Two of the most established scores are the Fong-Score described in 1999[229] and the more recent Genetic And Morphological Evaluation (GAME) score[230]. The Fong score involves lymph node status, preoperative CEA levels, disease-free interval within 12 months of CRC diagnosis, and number and size of CRLM. The GAME score incorporates molecular markers such as KRAS mutational status, the presence of extrahepatic disease, and the TBS (composite score of CRLM number and size, suggested to enhance correlation with OS as opposed to separate indicators of CRLM number and size[199]). A recent Dutch population-based study externally validating both CRS' concluded that their discriminative abilities are currently insufficient for adequate preoperative risk stratification[231]. The addition of a non-tumour related prognostic score (composite score of Alkaline Phosphatase, Albumin, mean corpuscular volume) to the Fong or GAME score was recently shown to improve the potential for prognostic risk stratification[232]. Overall, no prognostic score has yet reached a broad clinical application for personalised decision-making in patients with potentially resectable CRLM.

1.3 Fundamentals of thermal ablation

1.3.1 Microwave and radiofrequency ablation

MWA is based on a specific form of dielectric heating, induced by an electromagnetic (EM) field causing agitation of water molecules in the surrounding tissue. The oscillating electric charge from the EM wave causes polar water molecules to change direction, flipping back and forth 2 to 5 billion times a second, depending on the frequency of the microwave energy (Figure 7). This vigorous movement of water molecules trying to realign their electrical charge with the EM field, produces frictional heat and induces cellular death via coagulation necrosis[233,234].

Compared to RFA, MWA was shown to lead to more rapid heat production and creation of higher peak temperatures in *in-vivo* models [234–236], which was confirmed clinically by significantly faster ablation times[237]. MWA is also less influenced by passive heat conduction[238], resulting in improved performance near blood vessels. This is supported clinically by analyses of MWA for HCC, where no difference in LR rates was shown for lesions closely or distant from large intrahepatic veins[239]. For CRLM, clamping of the portal structures during MWA has been proposed to further reduce a remaining heat-sink effect in MWA[240]. Owing to the broader field of power density, MWA results in a larger zones of active heating allowing for more homogeneous volumes of cancer cell death[241].

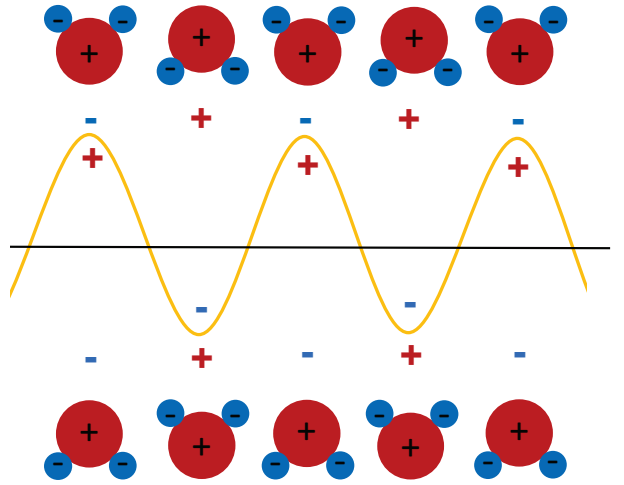

Figure 7. Physical property of heat creation during microwave ablation. The electromagnetic field causes rapid oscillations in the alignment of bipolar water molecules

Contrarily, RFA uses an alternating electrical circuit inducing electrical current between the ablation antenna and a grounding pad (monopolar mode) or between two interstitial probes (bipolar mode). Due to the abundance of ionic fluid, radiofrequency current is able to pass through tissue, however in an imperfect way, causing oscillations and collisions of ions and inducing resistive heating, also called the *Joule effect*. Direct heating occurs within millimetres of the applicator, while the rest of the ablation volume is created through thermal conduction into more peripheral areas around the electrode, causing denaturation of proteins and destruction of cell membranes[234]. RFA has been investigated and reported extensively for local destruction of primary liver cancer, where it represents the standard approach for very early and early stage (stage 0 and A) hepatocellular carcinoma (HCC) < 3 cm and not amenable to LT, and for downstaging of HCC prior LT, according to the Barcelona Care for Liver Cancer (BCLC) algorithm[242,243]. Its safety profile and limited efficacy for larger tumours are well established, as well as its use in combined treatment approaches e.g. together with TACE[244]. RFA is considered less suitable for lesions in proximity to larger intrahepatic vessels due to a phenomenon called *heat-sink effect*, where thermal energy is diminished via a cooling effect by the flowing blood, and suggested to increase the occurrence of LR at the ablation site[245]. This was supported by *in-vivo* experimental models[246,247] and in clinical studies, including a meta-analysis showing lower LR rates when performing RFA during hepatic artery occlusion[248].

Figure 8 summarises the physical properties, effects, advantages and limitations of RFA and MWA for the treatment of malignant liver tumours. Clinical results after MWA and RFA for CRLM are elaborated in more detail in chapters 2.1. and 2.3.

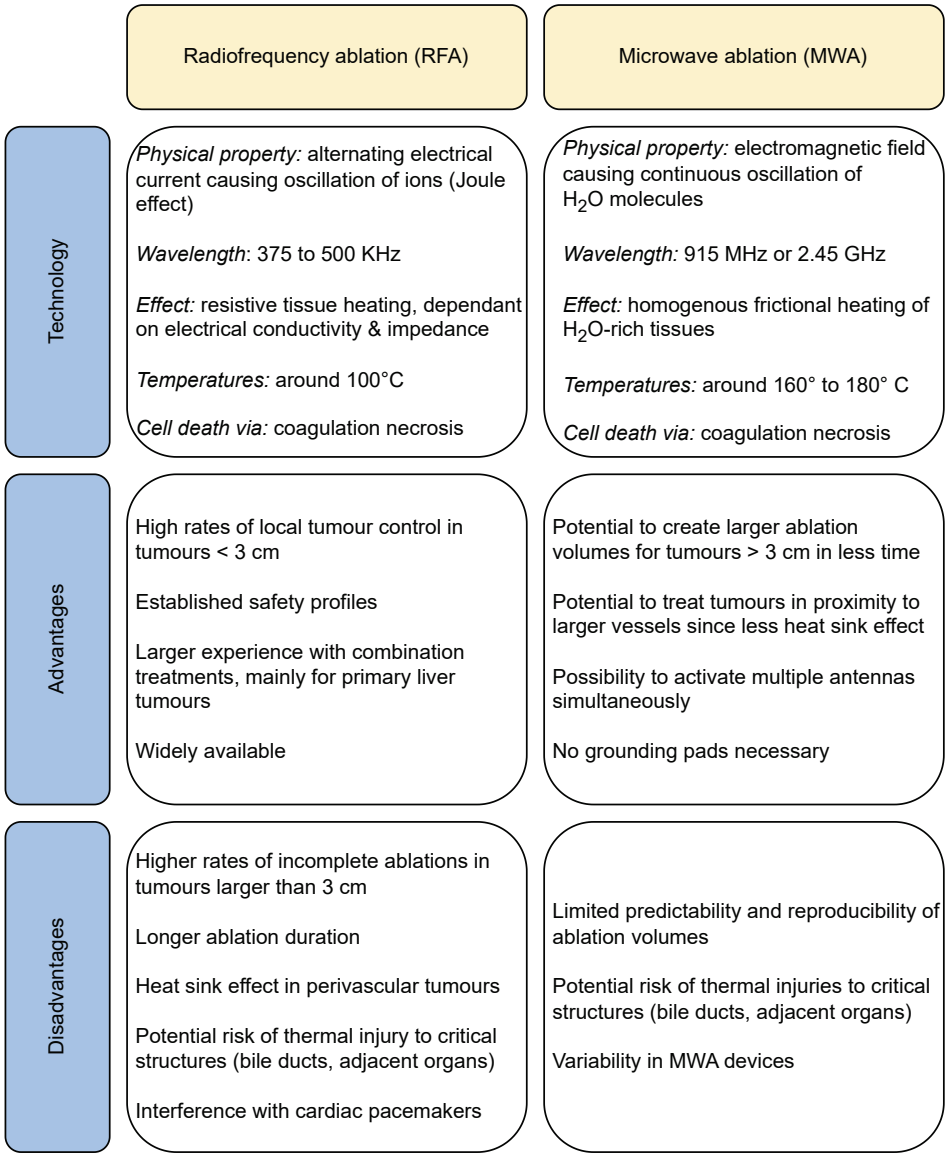

Figure 8. Physical properties, advantages and limitations of radiofrequency and microwave ablation for liver malignancies

In MWA, heat is propagated in a spherical manner away from the ablation antenna, creating mostly ellipsoid ablation volumes, as advertised by the ablation device manufacturers. More recent MWA technology employing higher frequency bands (2.45 GHz as opposed to 915 MHz) and more sophisticated EM field and wavelength control through saline irrigation, is claimed to create larger, more spherical and more predictable ablation volumes[237,249,250]. Nevertheless, the distribution of heat and resulting dimensions of created ablation volumes remain highly unpredictable. This is thought to arise from the

continuously changing physical tissue properties during ablation cycles, affecting impedance and thus heat production and ablation shapes[237], and is highly influenced by physical and chemical characteristics of the targeted tissues. These interactions are not clearly understood and remain poorly investigated to date. We have analysed factors related to the expansion of ablation energy and resulting effective ablation volumes (EAV) after stereotactic MWA (SMWA) of 116 CRLM in a recent study[251]. We confirmed poor predictability of created EAVs, which depend on other factors beyond the applied ablation energy, with only around 25% of the created EAV's explained by the applied ablation energy. On multivariable analysis, EAV depended on the tumour radius and KRAS-mutational status of ablated CRLM. The surface irregularity (ablation volume irregularity, AVI) of created ablation volumes was more pronounced when using higher ablation energies. Further studies using tissue sampling will allow to investigate the effect of steatosis e.g. induced by prior chemotherapy and of other physical properties such as the water-content of ablated tumours and the surrounding liver parenchyma. Dimensional aspects of AVI calculation and the investigated factors thought to affect ablation expansion and AVI are shown in Figure 9.

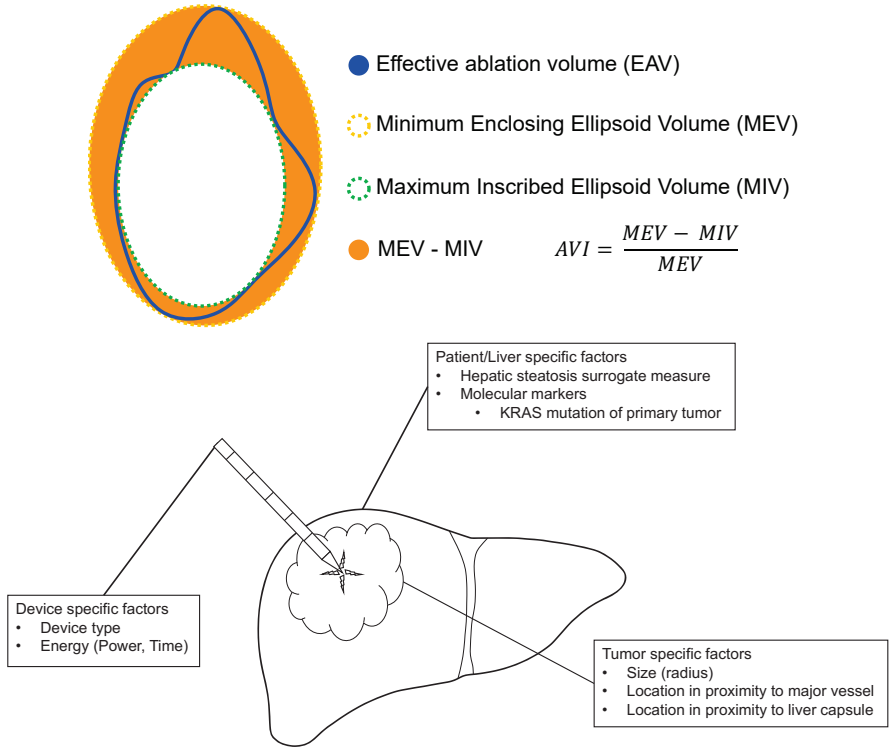

Figure 9. Calculation of created effective ablation volumes and ablation volume irregularities (top) and factors included in multivariable analyses investigating predictors of created ablation volumes (bottom). Reprinted with permission from [251] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

1.3.2 Treatment access and instrument guidance

TA of liver tumours can be performed using different treatment accesses as well as various imaging modalities for instrument guidance during the procedure. Traditionally, ablation was performed mainly by interventional radiologists for unresectable liver tumours or in patients that were non-surgical candidates, limiting TA to a percutaneous access[248]. With the more frequent application of TA as an adjunct or even alternative to resection, TA has increasingly been performed also by surgeons or in multi-disciplinary teams in the surgical or interventional radiology (IR) theatre. The principle of TA and general challenge to the clinician performing the intervention, is the placement of an ablation antenna at a specific position in or around the tumour. The target position is most frequently the centre of the tumour, when aiming for a single TA session. The precision with which the antenna placement is performed is independently related to the risk of LR at the ablation site and therefore warrants high-accuracy image-guidance[252]. Hence, optimal visibility not only of the target tumour but of the ablation antenna trajectory are required, to avoid injury to critical intrahepatic and perihepatic structures.

Most initial works on surgical TA of liver tumours reported an open surgical access, using intraoperative ultrasound (IOUS) guidance[253]. Ablation probe manoeuvring and freedom of access for precise antenna placement can be easier when compared to a laparoscopic approach, especially for tumours in superior dorsal liver segments[248]. Nevertheless, safety and efficacy of laparoscopic TA using laparoscopic IOUS for instrument guidance was shown[254–257]. The importance of a learning curve was highlighted in a recent study, where a significant reduction of incomplete ablation rates from 13% to 5% after 93 laparoscopic TA's was shown, even for tumours located in the superior dorsal segments[258]. In an IR setting, TA is traditionally performed using US imaging for instrument guidance, due to several merits over other imaging modalities such as its real-time imaging capability, lack of radiation exposure, easy accessibility and low cost[259,260]. Drawbacks include a limited tumour visibility in lesions located centrally or in altered liver parenchyma e.g. after extensive chemotherapy[261], from shadowing artefacts caused by air, bone or bowel, and its subjectivity prone to high intra- and inter-operator variability[262]. Nevertheless, local tumour control rates over 90% were shown with modern US technology or contrast-enhanced US (CEUS) for percutaneous TA[263,264]. The use of CT or MRI for image-guidance allows to overcome some limitations of US guidance, leading to highly effective and safe TA of CRLM[265–268]. Drawbacks include potential high radiation exposures or limited feasibility due to MR-incompatible equipment or conditions[269]. Image-fusion combining real-time US with CT/MRI/PET-based reference imaging shas shown promising results, facilitating mental reconstruction of two-dimensional images, enhancing conspicuity of CRLM and allowing to target lesions invisible on US imaging[270–273].

The choice of treatment access is optimally based on the overall patient's treatment strategy, applying the most MI approach allowing a safe and oncologically effective ablation, rather than on sub-speciality-driven indication[274]. When a percutaneous treatment access is not feasible, a laparoscopic access should thus be preferred over an open approach. Reasons for a surgical rather than an interventional access include

combined surgical strategies of CRLM ablation and resection or synchronous resection of the primary CRC tumour, the need for simultaneous diagnostic laparoscopy or to address multiple (> 5 tumours)[275]. The latter scenario might warrant high levels of contrast agent or procedural complexity in an IR setting. A proximity of subcapsular lesions to adjacent visceral organs such as the stomach or colon or the diaphragm have been addressed with hydro or pneumo-dissection or balloon interposition techniques[276], but might also be easier accessible laparoscopically. The direct comparison of treatment approaches for TA of CRLM identified a percutaneous access as an independent risk factor for LR in earlier works[248,277]. Differences potentially arose since different ablation margin were sought in an IR setting (0 mm) and in the surgical setting (10 mm). More recent data including a systematic review reported 5-year OS rates of 30%, 28% and 21% when using a percutaneous, laparoscopic or open approach for ablation of CRLM, along with decreasing mortality, morbidity and LOS and similar ranges of LR rates[274]. Others confirmed a lack of influence of the treatment access on complications, local tumour control and survival rates after TA of hepatic malignancies and of CRLM specifically[278,279].

The efficacy of using a percutaneous IR treatment access for TA of CRLM has improved significantly over the last 10 years[280]. For an optimal assessment of technical success after TA for CRLM, it was advised to perform a CE-CT imaging immediately or shortly after treatment, or if not available or contraindicated, an immediate CEUS followed by CE-CT within 3 weeks[281]. The first imaging after TA will serve as the baseline for further assessment of local tumour control and potential detection of subsequent LR. A CE-CT or MRI 3 to 8 weeks after TA is advised to confirm a complete ablation of the treated tumour (technique efficacy)[281,282].

1.4 Innovation technology for thermal ablation

Despite advances in the quality of modern imaging modalities, patients with liver tumours oncologically qualifying for TA are often not amenable to safe TA using a MI treatment access in the clinical reality. Reasons include an intrahepatic tumour location which is challenging to access, or insufficient tumour visibility. In an IR setting, *difficult-to-target* tumour locations include the liver dome[283], a subcapsular location, proximity to the liver hilum with its main vascular and biliary structures, to the caudate lobe[284] or to the heart[285,286]. In a laparoscopic setting, the visualization of both the laparoscopic IOUS and the ablation antenna in one image plane can be challenging, particularly in the superior dorsal liver segments[287]. In these situations, additional stereotactic instrument guidance may enhance eligibility to safe and precise TA targeting, especially in a MI setting.

Precise ablation antenna positioning is key for safe TA, however, the success of TA treatment ultimately depends on the ablation energy expansion and resulting ablation volumes adequately covering the target tumour. Innovative algorithms investigating the predictability of ablation energy expansion (see also chapter 1.3.1) and for quantitative analysis of ablation margins (see also chapter 1.4.2) might enhance efficacy and

reproducibility of successful TA of malignant liver tumours. Overall, the aim of developing innovative technology for TA is an optimisation of the procedural performance in terms of eligibility, safety and efficacy through enhancing accuracy, predictability and standardisation of ablation techniques.

Figure 10 summarises components of successful TA and areas where innovation technology can enhance the success of safe and effective TA of malignant liver tumours.

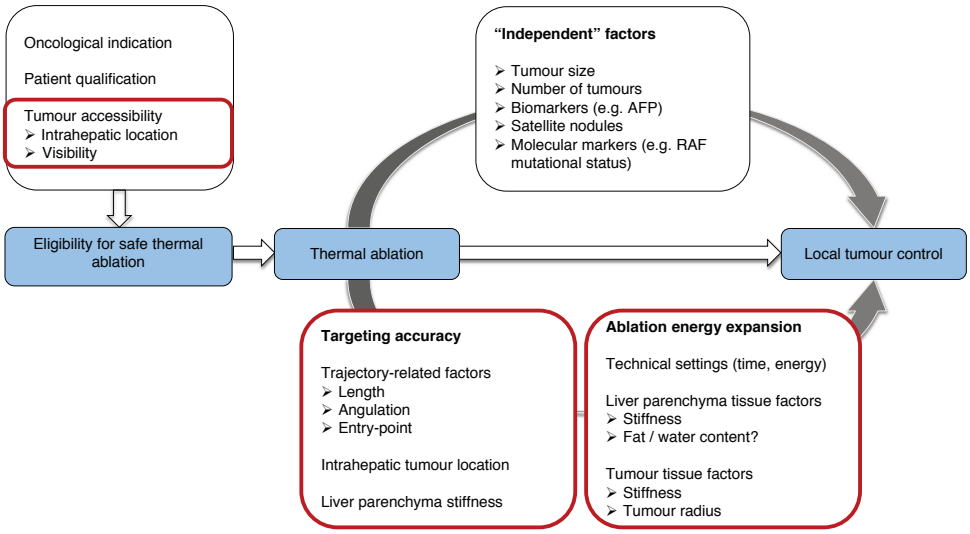

Figure 10. Components of successful thermal ablation of malignant liver tumours. Areas where innovation technology can enhance eligibility, safety and efficacy of thermal ablation of liver tumours are highlighted in red

1.4.1 Stereotactic navigation technology

The overall aim of computer-assisted stereotactic navigation is to provide additional information on the exact localisation of a target as well as the position of instruments in the operating space. Similar to a global positioning system (GPS) for vehicles or airplanes, the goal is to provide enhanced guidance information for the planning and pursuit of optimal trajectories to improve navigational precision.

For TA of liver tumours specifically, image-guided navigation aims to i) optimize precision in the positioning of the ablation probe and ii) enhance safety, by defining a trajectory that minimizes damage to important structures and by minimising the number of required ablation probe insertions and manipulations[288,289]. In a series of over 300 consecutive SMWA treatments of malignant liver tumours, we showed that the precision of antenna placement (targeting accuracy) was independently associated to the incidence of LR[252]. Factors influencing targeting accuracy on multivariable analysis were cirrhosis in patients with HCC and the targeting trajectory length, both reflecting a potential shift in the target

position during antenna insertion resulting in imprecisions in the navigational information. Importantly, the location of tumours in "challenging" intrahepatic positions (Segments VII, VIII or Segment I) had no influence on targeting errors or the LR rate when using stereotactic navigation technology, highlighting its potential to enhance eligibility for safe and effective TA treatment in such situations. Overall, targeting precision was very high with a mean target positioning error of 2.9 +/- 2.3 mm[252]. Example cases of SMWA for tumours located in challenging intrahepatic positions are shown in Figure 11 and Figure 12.

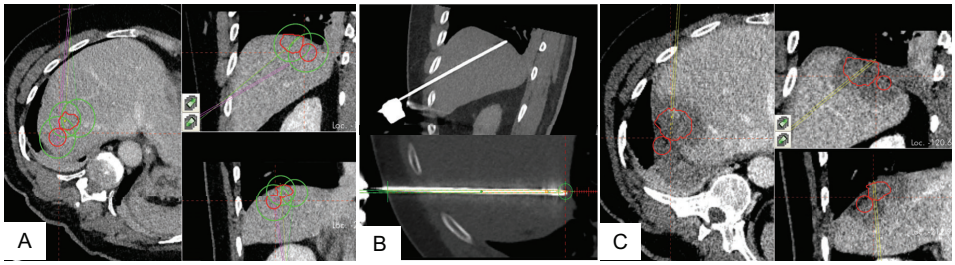

Figure 11. Clinical example case of two adjacent hepatocellular carcinoma lesions (red) located in segment VII treated with stereotactic microwave ablation. A) Planning of targeting trajectories for 3 parallel ablation probes to create overlapping ablation volumes (simulated in green). B) Validation of ablation probe position in a subphrenic position. C. Validation of complete tumour ablation with an adequate ablation margin. Reprinted with permission from[290] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

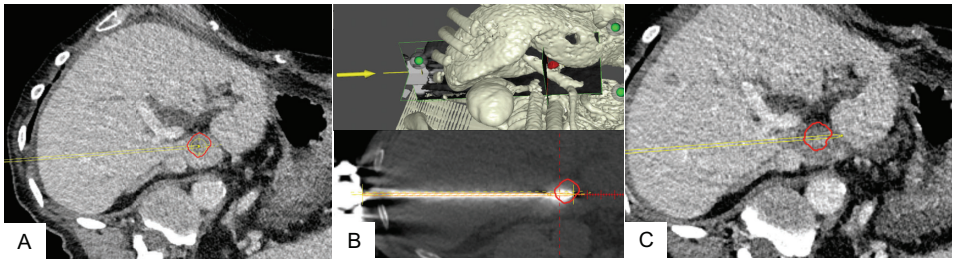

Figure 12. Clinical example case a colorectal liver metastasis (red) located in segment I treated with stereotactic microwave ablation. A) Planning of the targeting. B) Validation of the ablation antenna position. C) Complete tumour ablation and patent adjacent main portal vein structures. Reprinted with permission from[290] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

The use of stereotactic navigation in surgical procedures of solid organs was first described for neurosurgery and has since found applications in a number of surgical disciplines, including orthopaedics, otorhinolaryngology and liver surgery in the late 1990ies[291]. To date, image-guided navigation systems used for liver interventions are mostly based on a process called *registration*, where image-data (3D reconstructed CT imaging) is brought into overlay with the intraoperative real-time target organ position, within a measurable coordinate system. This is done by defining surface or internal landmarks, visible on both the image data and the patient organ or surface, and will allow the spacial tracking of co-registered structures and instruments[292]. Different types of tracking and coordinate systems are available, such as optical or EM-based tracking. With

optical tracking, an infrared camera recognises reflecting markers on instruments and surfaces, providing the navigation system with the required spacial information on the respective structures. This requires a direct line-of-sight, which can be a disadvantage when the instrument tip (e.g. ablation antenna tip) is located distantly from the extracorporeal markers, and instrument bending may introduce navigational imprecision. Using EM tracking technology allows to attach trackers to flexible or bending instruments, permitting a more dynamic tracking within an EM coordinate system without requirement of a direct line-of-sight[293,294]. On the other hand, EM tracking requires the target organ and patient to be placed within an EM field, which is subject to disturbances from ferromagnetic material in its vicinity, which can introduce navigational imprecision[295].

In a laparoscopic setting, a number of different image-guided navigation systems for liver surgery have been assessed *ex-vivo*[295–299], but clinical studies applying such technology remain scant to date[300–304]. In a series of 75 consecutive patients treated with navigated laparoscopic TA for with 346 malignant liver tumours at two European centres, we showed that navigated laparoscopic TA was safe, with major complications below 5%, even when targeting multiple (up to 25) tumours in one treatment session[287]. An additional time effort of 4.30 minutes was required for image-to-patient registration, confirming a minimal disruption of the overall surgical workflow by applying navigation technology. Using CT imaging dated prior to neoadjuvant chemotherapy for registration, further allowed the treatment of 51 DLM not visible on IOUS or on the latest CT imaging[287]. Figure 13 and Figure 14 show the set-up and navigated targeting during laparoscopic navigation in liver surgery.

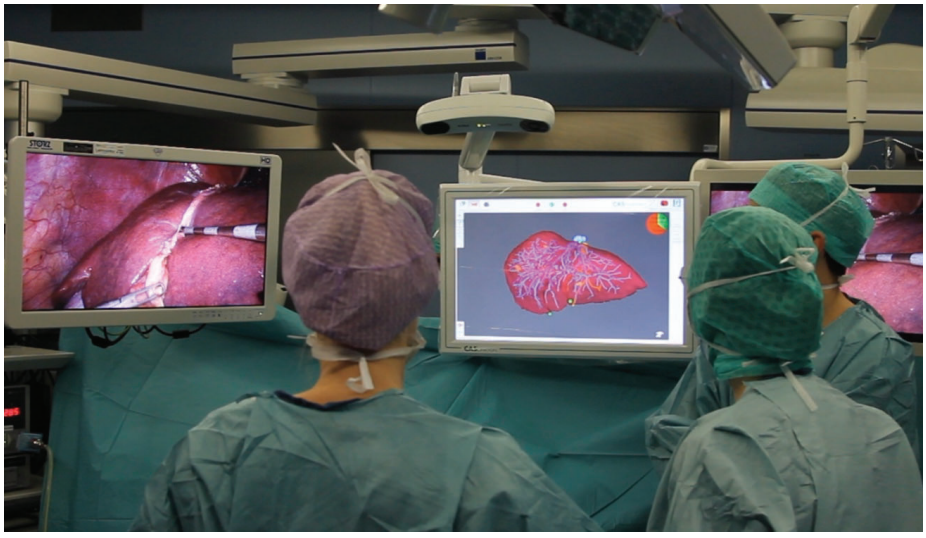

Figure 13. Set-up in the operation theatre for laparoscopic navigation. The infrared camera overlooks the surgical site, tracking co-registered surgical instruments. The process of image-to-patient registration is shown, with selected surface points on the 3D reconstructed image of the patient liver (right screen) being indicated on the real-time patient liver with a laparoscopic pointer (left screen)

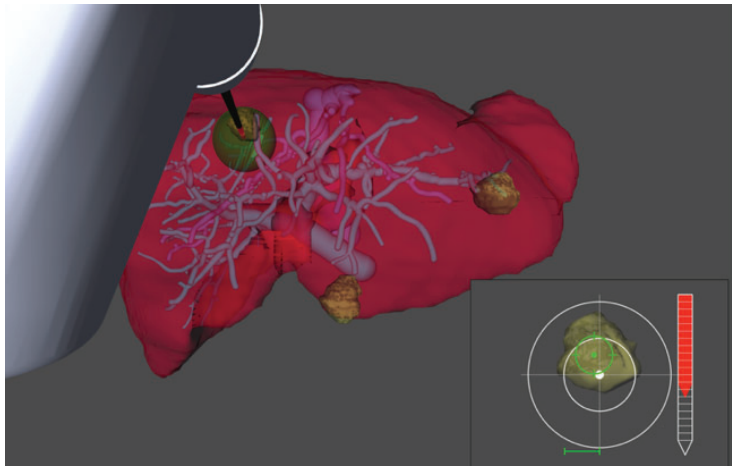

Figure 14. Navigated targeting of the intrahepatic tumour in the 3D reconstructed image. The co-registered ablation antenna is inserted towards the intrahepatic tumour target using a crosshair viewer (bottom right) indicating the trajectory direction and the depth of the targeted tumour. The size of a spherical ablation volume is simulated at the tip of the ablation antenna (green)

One of the main drawbacks in image-guided, surgical soft-tissue navigation is the imprecision in guidance information arising from organ deformation during the procedure. After image-to-patient registration, every displacement of the intraoperative liver position, e.g. during organ mobilisation or by deformation of the liver surface by the IOUS probe, leads to errors in the registered image points. This is enhanced when using pre-operative imaging for registration, where the liver shape might not correspond to its intraoperative shape and position, e.g. after introduction of a pneumoperitoneum, even prior to mobilisation and manipulation of the liver. Promising attempts to adapt for organ deformation have been made, including the use mathematical algorithms or the integration of augmented reality, but none have yet been established in a clinical routine[305,306]. Hence, the use of surgical navigation on a broader clinical scale has not yet had a major breakthrough. A more dynamic method trying to bypass imprecision by organ deformation, using EM-tracked laparoscopic IOUS-based point-to-point targeting for TA navigation, showed reproducible targeting errors below 5 mm in an *ex-vivo* setting[295].

Contrarily, IR represents the optimal environment for image-guided navigation using landmark-based image-to-patient registration with optical instrument tracking[307]. With patients under general anaesthesia and positioned securely e.g. on a vacuum mattress, this static situation allows an optimal co-registration of immediate CT imaging to the patient's liver position[292]. Using high-frequency jet ventilation for patient ventilation allows further reduction of liver displacements by reducing breathing motion of the diaphragm to a minimum[308]. The workflow of SMWA using one of the commercially available navigation systems (CAS-ONE, CAScination AG, Switzerland) includes i) a planning phase, where optimal ablation antenna trajectories are selected on a first co-registered CE-CT scan, ii) a navigation phase, where an optically tracked aiming device is aligned with the previously defined antenna trajectory, followed by ablation antenna introduction, iii) a

validation phase where the adequate position of the positioned ablation antenna is verified in a second co-registered native CT scan, followed by the actual MWA treatment, and iv) an ablation validation phase, where the treatment success with adequate overlay of the ablation volume over the target tumour is verified in a third co-registered CE-CT scan (Figure 15)[252,307]. Performing such procedures in a multi-disciplinary team of interventional radiologists and hepatobiliary surgeons allows an optimal integration of clinical, procedural and oncological aspects during the treatment of malignant liver tumours.

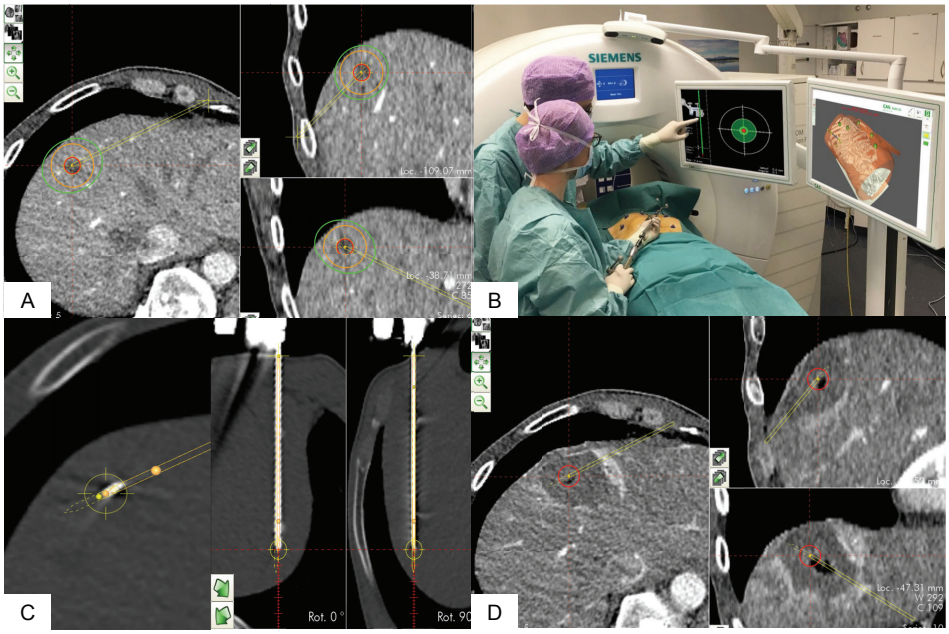

Figure 15. Workflow of stereotactic microwave ablation using the CASOne navigation system. (A) Planning of optimal ablation antenna trajectories by selecting target and entry point on the CE-CT planning scan, red: target tumour, orange: planned ablation margin, green: simulated ablation volume. (B) Navigated alignment of the aiming device along the planned trajectory using a cross-hair viewer indicating the trajectory direction and a depth indicator in millimetres for ablation antenna insertion. (C) Validation of the positional accuracy of the ablation antenna relative to the planned trajectory, prior to applying microwave ablation treatment. (D) Validation of the created ablation volume by direct overlay of pre- and post-ablation CE-CT images, allowing immediate estimation of technical success. Reprinted with permission from[252] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

We performed a systematic literature review and meta-analysis on studies reporting procedural and clinical outcomes of stereotactic or robotic TA of malignant liver tumours in a MI setting[309]. Thirty-four studies (two RCT, three prospective cohort studies, 29 case series) treating different entities of malignant liver tumours were included. While earlier works focused mainly on technical and procedural aspects such as safety, accuracy and efficiency of the intervention, later works published after 2017 increasingly reported treatment efficacy. In summary, a pooled mean lateral targeting error of 3.7 mm

(Confidence interval (CI) 3.2 to 4.2 mm, with significant between-study heterogeneity) (Figure 16), a range of procedural durations of 18 - 255 minutes, total radiation doses of 807 to 2216 mGycm and a pooled major complication rate of 2.4% (CI 1.4 to 3.6%), were reported. The pooled mortality rate was 0.8% (CI 0.4 to 1.4%). Rates of technical success, primary and secondary technique efficacy and LR ranged between 90 to 100%, 81 to 100%, 90 to 100% and 0 to 54%, respectively. Variability in applied definitions, inclusion criteria and treated tumour entities limited the comparability of studies.

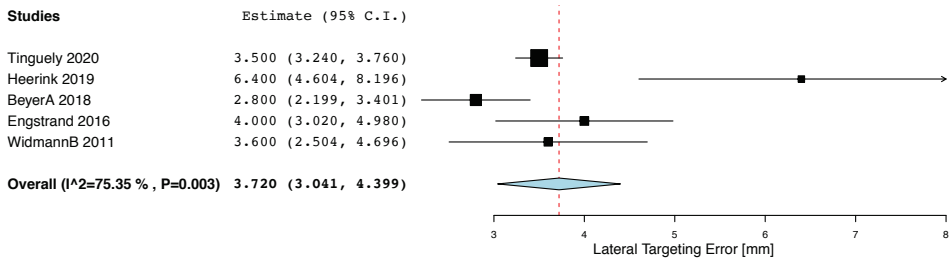

Figure 16. Weighted average of reported targeting accuracy defined as lateral targeting error in millimetres. Reprinted with permission from[309] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

The only available work reporting stereotactic TA specifically for patients with CRLM, was a retrospective series by Bale et al.[310], with 63 patients undergoing navigated RFA of 189 CRLM lesions. The primary success rate evaluated at 1 month was 93.1%, with ten patients being retreated, yielding a secondary efficacy rate of 99%. Thirty-one (16%) of patients developed LR at further follow-up (median follow-up time 25 months). Most lesions (70%) were smaller than 3 cm, however 12% were lesions between 5 and 13 cm, potentially contributing to the high rate of major complications (17%) in this series. Importantly, 41% of patients were considered potentially resectable, and the OS rates at 1-, 3- and 5-years of 92%, 66% and 48% in this patient subgroup were encouraging.

1.4.2 Software algorithms for treatment evaluation

Treatment success of TA depends on a full coverage of the targeted tumour by the ablation energy and the resulting ablation volume. As in surgical resection, a safety margin between the tumour surface and the ablation volume surface is desired to decrease the probability of incomplete ablation and LR. In surgical resection, a resection margin of 1 mm has been defined as the cut-off to distinguish between R0 and R1 resection[311], with even sub-millimetre margins being proposed in patients with good tumour biology[312]. In TA, controversies exist in the definition of the optimal "A0" margin for TA. An independent association between the size of the ablation margin and LR after TA has been confirmed, and a preferred margin size of 5 to 10 mm proposed[255,256,281,313,314]. KRAS mutational status was shown to affect the impact of smaller ablation margins on LR, implying a potential heat resistant mechanism of KRAS mutated tumour tissue[315,316].

Regardless of the margin definition, reporting 2-dimensional ablation margins by visual inspection is subjective and prone to inter-reader variability, lacking an accurate quantitative and volumetric knowledge of ablation margins[317]. Software algorithms for 3D margin assessment in a quantitative manner have therefore been proposed, aiming to standardise the reporting and comparison of treatment success after TA. While most existing reports focused on average minimal ablation margins (MAM)[318–322], we have created a novel algorithm for 3D quantitative ablation margin (QAM) computation, allowing the reporting of quantitative distributions of ablation margins after TA[323]. The algorithm for stepwise computation of 3D QAM is illustrated in (Figure 17). An adapted algorithm for QAM computation for tumours located in a subcapsular position treated with TA was further proposed, accounting for the underestimation of calculated QAM in these situations[323]. Applicability of the QAM metric was confirmed in clinical example cases of CRLM treated with SMWA, and the computational code made publicly available. The proposed QAM algorithm served as the base for in-depth analyses of factors affecting ablation energy expansion and LR after SMWA for CRLM in Study II.

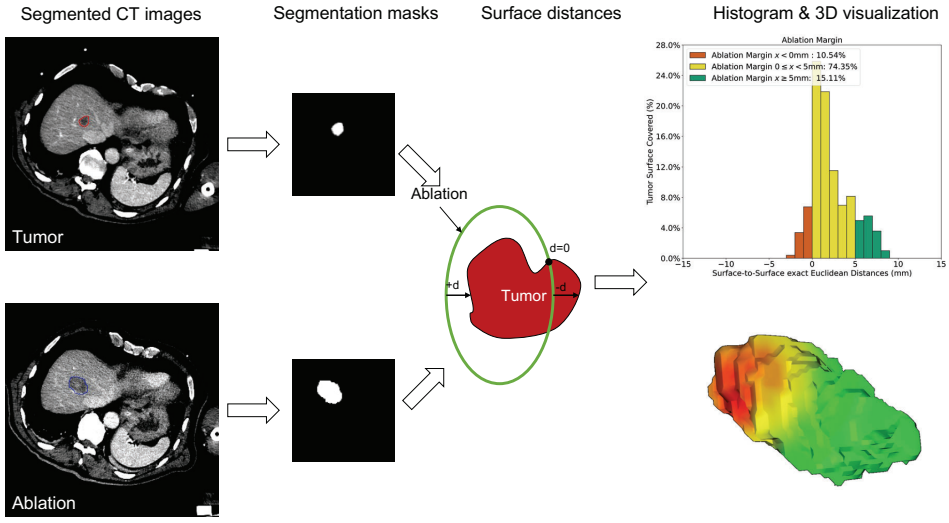

Figure 17. Stepwise algorithm for the generation of quantitative ablation margins (QAM). From pre- and post-ablation CT images, the tumour and ablation volumes are segmented and extracted. Euclidean distance maps between the ablation and tumour volume surfaces are calculated in 3D and displayed as relative distributions of QAM distances in a histogram, colour-coded for margins < 0 (red), 0 to 5 (yellow) and > 5 mm (green), or as a reconstructed ablation volume with a respectively coloured surface. Reprinted with permission from[323] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

2 Literature review

2.1 Thermal ablation for colorectal cancer liver metastases

Since the first applications of TA for the destruction of liver tumours in the 1980ies[324], RFA and MWA have become well-established treatment modalities for malignant liver tumours including CRLM[135,281,325]. With increasing experience of performing TA leading to improved clinical and oncological outcomes, and cumulative evidence that patients with OMD benefit from locally aggressive treatments, indications for TA were widened. TA is now part of the toolbox of local ablative strategies aiming to achieve a state of NED and long-term disease control in patients with OMD (see also chapter 1.2.3.3)[281,326,327].

Technical success rates (complete tumour ablation as assessed on the first post-ablation imaging) were reported between 93% and 100% after TA of CRLM[263]. The amount of studies reporting local tumour control and long-term oncological outcomes after TA for CRLM have significantly increased but are reported controversially over recent years. While higher rates of LR after TA of CRLM as opposed to resection was often highlighted, others report similar rates[278,328–330]. Overall, the range of reported LR rates vary widely between 4% and 60%[331–333]. A recent systematic review and meta-analysis including 12 studies on RFA and 6 studies on MWA for CRLM showed a pooled median local tumour progression rates of 18% (1% to 37%)[334]. The wide variety can partially be explained by variations in the terminology used to describe LR, and differing follow-up definitions and time points of follow-up after TA. A consensus paper for the reporting of outcomes after TA was proposed by Ahmed et al[335], however some definitions remain blurry especially regarding the time points of follow-up assessment[309]. Reported OS rates after 3 and 5 years range between 14% to 91% and 14% to 58%[253,278,342,330,332,336–341], varying widely partially due to heterogeneity of included patient groups. In two recent meta-analyses summarising outcomes after MWA for CRLM in 12 and 20 studies, respectively, pooled median 3 and 5-year OS rates of 60% to 70% and 45% to 55% were described[334,343].

The main strengths of TA in CRLM treatment are linked to its parenchyma-sparing features, destroying the targeted tumours locally and preserving a maximum of surrounding liver tissue. The possibility of performing TA using a MI treatment access further reduces treatment-related morbidity and associated recovery times and LOS. Accordingly, major complication rates after thermal ablation for CRLM are reported to range between 1.3% and 16%[263,336,337,344–346]. The recent meta-analysis of Di Martino et al.[334] reported a pooled median major complication rate of 1.5% (0 to 5%) and 0 (0 to 13%) after RFA and MWA of CRLM, respectively. Overall complication rates were 8% (0 to 25%) after RFA and 7% (7% to 14%) after MWA[334]. Higher major complication rates were reported after TA of CRLM in close vicinity of the main bile ducts[241]. Such a peri-hilar tumour location, especially after previous major hepatectomy, were therefore stated as contraindications for TA of CRLM in a recent consensus statement[326]. Median durations of LOS were in the range of 1 to 3 days[174,237,274,347]. Reports on QOL after TA for CRLM are currently scarce[348,349] (see also chapter 6.1).

The highest level of evidence regarding the use of TA for CRLM was shown in a phase II RCT, where aggressive local RFA (with or without resection) combined with FOLFOX significantly prolonged OS compared to chemotherapy alone (5-year OS 43% versus 30%) in patients with unresectable CRLM[73]. Other non-randomised trials have confirmed a significant prognostic improvement after TA for tumours up to 3 cm when compared to chemotherapy alone[327,350]. The reported literature on TA for potentially *resectable* CRLM within curative-intent treatment strategies, is more heterogeneous and based on data from observational studies. The comparability of studies in available meta-analyses on treatment-related and oncological outcomes after TA of CRLM are therefore limited. TA was shown to be beneficial in terms of morbidity, cost effectiveness and OS as adjunct to surgical resection for patients with more extensive disease[127–129,327,351–355], also compared to more aggressive two-stage resection procedures in bilobar disease[119,356–359]. For recurrent intrahepatic CRLM after resection, TA is well tolerated without compromise of long-term prognosis in terms of LR, RFS and OS[174,360,361]. The role of neoadjuvant chemotherapy prior to repeat TA is controversial[362]. Generally, best results are achieved for lesions ≤ 3 cm in size and up to 5 in number, however several expert recommendations widen TA indication for lesions up to 5cm and for more lesions in selected patients[274,326]. Recent international guidelines recommend TA for potentially resectable CRLM and thus treatment with "curative intent", as follows:

- The latest European Society for Medical Oncology (ESMO) guidelines[63] state that the indication for TA currently consist of i) a useful adjunct in combination with resection to achieve complete tumour control, ii) an alternative to resection in patients inoperable due to frailty or difficult anatomical CRLM location, iii) within the toolbox of local treatments for OMD, if a "widely invasive surgical approach is required", and iv) as valid treatment option for recurrent CRLM after resection
- The Shanghai consensus[363] and the Chinese guidelines[364] recommend the use of TA for i) potentially R0 resectable CRLM to achieve NED when hepatectomy is technically difficult, in combination with resection alone, ii) in combination with resection in the treatment of multiple bilobar disease, iii) for patients unsuitable or unwilling to undergo surgery and iv) for the treatment of recurrent CRLM
- The latest NCCN guideines version 2.2023[365] do state TA as an alternative to resection, with resection being preferred, for resectable synchronous and metachronous CRLM, alone or in conjunction with resection, in patients with OMD that may not be optimal condidates for resection

Few local treatment guidelines mention TA as part of the management of patients with resectable CRLM[130,366,367]. A recent consensus paper by the COLLISION Trial (NCT03088150) study group has defined "ablatability" criteria for TA with curative intent, considering the intrahepatic tumour distribution and lesion size[326]. They suggest TA for potentially resectable CRLM up to 3 cm if less than 3 lesions and located centrally, requiring major hepatectomy if treated with surgery. They further suggest TA for CRLM up to 5 cm if they are unresectable due to anatomical location. Ongoing prospective registries such as the CIRSE Emprint Microwave Ablation Registry (CIEMAR) aim to investigate the "real-time" use of MWA for CRLM on a broader scale (NCT03775980).

With growing literature available on TA for CRLM, analyses on clinical, tumour and treatment-related factors associated with oncological outcomes after TA are available. One of the most important factors for successful TA is complete ablation with a sufficient ablation margin (see chapter 1.4.2). The other parameter found to affect the incidence of LR most consistently is tumour size above 3cm, with a significant increase in tumour recurrence and OS after TA for larger lesions. The association between proximity to larger intrahepatic vessels and LR is mainly shown after RFA[265,368], but is reported inconsistently after both MWA and RFA treatment[253,265,369–371]. Factors found to influence LR and OS in multivariable statistical models or in consensus papers are summarised in Table 2. Studies reporting RFS or DFS with tumour recurrence at any site were excluded. One often encountered problem in the statistical methodology of works investigating LR rates in multivariable analyses on a per-tumour basis, in patients ablated for several lesions, is the failure to include repeated measure-analyses or mixed models accounting for the hierarchical structures of patient and lesion-specific characteristics. Another frequently neglected issue is the phenomenon of *immortal time bias* when analysing time-to-event outcomes for repeated treatments, leading to bias in favour of the treated group (e.g.[372] describing prior hepatectomy as a beneficial factor for LR after TA)[373]. This even precipitates some authors to question the legitimacy of available evidence supporting an aggressive local treatment (resection or ablative treatments) for patients with CRLM within the definition of OMD[374,375].

	Local recurrence	Overall survival
Clinical factors		
Number of tumours	376–379	84,274,369,376,380–384
Tumour size	237,248,385–387,253,278,280,346,369,377–379	274,369,376,380,381,383–385,388
Bilobar tumour distribution		388
Tumour proximity to vessels	253,265,368	
Right versus left-sided primary tumour		380,382
No prior hepatectomy	346,372	
Clinical risk score (Fong et al[229])		369
(Response to) Chemotherapy	84,280,378,379	84,383
Histopathological factors		
Nodal status of primary tumour	280	
Histopathological growth pattern	333	
Laboratory parameters		
CEA level	389	310,381,383,384
Lymphocyte-to-monocyte ratio		385
Neutrophil-to-lymphocyte ratio		390
Genomic alterations		
KRAS oncogene	372,391	316,382
Cancer-related signalling pathways	376	
Procedural factors		
RFA versus MWA	237	
Percutaneous treatment access	248,280,343,392	
Ablation margin	265,316,391,322,325,346,372,376–378,387	

Table 2. Factors associated with increased local recurrence and shorter overall survival after thermal ablation of colorectal cancer liver metastases identified in multivariable regression models

2.2 Thermal ablation versus surgical resection

Encouraged by improving outcomes after TA for CRLM, the question whether it might be a valid alternative for potentially resectable CRLM has been discussed increasingly. In the current literature, the vast majority of research comparing TA to surgical resection for CRLM arises from observational studies. The only available RCT comparing TA versus resection comes from Japan in the year 2000, reporting similar OS after MWA and resection for resectable CRLM[393]. However, the few (n = 30) patients included in this study, an unclear randomisation method and one fourth of patients not included in the absence of an intention-to-treat analysis, warrant caution regarding the validity of results.

A systematic literature search in Pubmed performed on March 20, 2023, using the search terms: "(thermal OR microwave OR radiofrequency) AND ablation AND (versus OR compar*) AND (resection OR hepatectom* OR surgery) AND colorectal AND (liver OR hepatic)" yielded a total of 451 studies. After screening titles and abstracts for studies comparing TA to resection for patients with CRLM, excluding combined resection and TA techniques, 54 studies remained. The two studies being part of this thesis were removed (study I and III), leaving 52 studies, of which 19 were reviews or meta-analyses, and 33 were original research papers, published with increasing frequency over time (Figure 18).

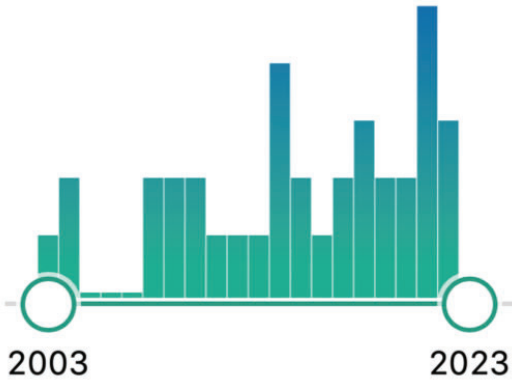

Figure 18. Trend over time in the published literature comparing thermal ablation to resection for colorectal cancer liver metastases. Extracted from https://pubmed.ncbi.nlm.nih.gov

Of the original research papers, all papers were retrospective analyses, mostly case series, with seven propensity-score matched analyses[338,360,394–398] and three cost effectiveness-analyses modelling data extracted from the literature[399–401]. Twenty-six studies reported on RFA as the TA modality, 2 on MWA and 5 on both RFA and MWA as opposed to surgical resection for CRLM treatment. Results including peri-operative outcomes, recurrence pattern and OS of the 33 studies are summarised in Table 3. Overall, the majority of studies reported equal or lower morbidity rates with TA, shorter LOS with TA, equal or higher rates of local and overall recurrences, and equal OS rates. The latter was also the case in studies which investigated the effect of treatment type on OS in multivariable regression analyses. The seven studies using propensity-score analyses to address

confounding and selection bias, unanimously showed equal OS after TA and resection. Recurrence rates, RFA and DFS were reported varyingly, one study comparing TA or resection both after neoadjuvant chemotherapy even reporting longer RFS with TA.

Type of study	Overall morbidity	Length of hospital stay	Local recurrence	RFS/ DFS	OS	Cost effective-ness
Propensity-score matched						
Favouring TA	338,394,396	360,395,396		360		
Favouring resection			338,394,396,397	397		
No statistical differences	360,395,398		395,398	338,394,395,398	338,360,394–398	
Cox regression-based*						
Favouring TA	254,347,402–405	174,254,347,403–405				
Favouring resection			403,406,407	403,405–408	406,407,409	
No statistical differences	174,407,409–412	410,412	174,402,408,409,411	174,254,347,402,404,409,411,412	174,254,347,402–404,408,411–413405	
Non-matched non-adjusting*						
Favouring TA	407	414,415				
Favouring resection			415		416	
No statistical differences	414,417		416–419	415,417,418	414,415,417,418	
Other						
Favouring TA						399,401
Favouring resection						400
No statistical differences	401		401	401	401	

Table 3. Outcomes after thermal ablation versus resection in 33 studies identified in the literature search. *With regard to overall survival analyses. Light blue: 1 to 3 studies, Mid-blue: 3 to 5 studies, Dark blue: 5 or more studies. In studies with subgroup analyses stratified by tumour size, the outcomes for tumours < 3cm are reported[398,402,404,411,416]

Three PS-matched studies comparing outcomes after TA for technically *resectable* CRLM with resection, reported 3-year OS from 60 to 72% after TA versus 67 to 74% after resection, and 5-year OS of 43 to 48% after TA and 54 to 55% after resection[338,397,398].

Several recent systematic reviews and meta-analyses are available comparing outcomes after TA and resection[126,148,344,420–424]. Most earlier and some recent summary papers ranked TA as inferior to resection in terms of recurrence and OS[334,420,425–427]. Methodological limitations of direct comparisons were stressed more recently, highlighting the relevant selection bias in analysed studies typically comparing outcomes after TA for *unresectable* CRLM with results after resection for *resectable* CRLM[344,422]. This leads to *confounding by indication*, where the very reason why TA was chosen partly causes the impaired survival

reported in these patients. This makes the validity of a direct comparison and pooled analyses of patients treated with TA versus resection questionable. More recent works acknowledged these issues and carefully adapted the methodology of performed meta-analyses. Meijerink et al.[350] systematically assessed bias in the available literature and reported results according to corresponding evidence levels. They showed that with *very low* grade evidence levels, i) RFA alone (for unresectable CRLM) is inferior to resection alone, MWA alone is equivalent to resection alone in terms of OS, ii) RFA alone was inferior versus resection alone in terms of LR and DFS, and iii) RFA alone was superior to resection alone, while MWA was equivalent to resection with regard to complications[350]. Hao et al.[423] performed meta-regression to identify causes of heterogeneity between included studies and adapted subgroup meta-analysis accordingly. They showed that 1-year RFS and 3-year OS were similar after TA and resection for tumours smaller than 3cm, and 5-year OS was similar in studies published after 2011[423]. Contrarily, other meta-analyses comparing TA versus resection for CRLM < 3cm specifically showed inferior RFS and OS after TA[344,428]. Alike most meta-analyses, the latter studies showed significantly decreased morbidity with TA, and specifically also for wound and biliary complications[344]. Overall, the literature provides conflicting results, at least partially due to inclusion bias and between-study heterogeneity, and potential differing technical and operator factors[429].

To date, no results from well-powered prospective comparative studies or RCTs are available comparing TA to surgical resection for patients with CRLM. A UK-based trial (LAVA trial) was prematurely terminated in the past due to failure to recruit, stating "misconceptions about the eligibility criteria for the trial, surgeons' preferences for one of the treatments ('lack of clinical equipoise' among some of the surgeons in the centre) with unconscious bias towards surgery, patients' preference for one of the treatments, and lack of dedicated research nurses for the trial" as the key issues inhibiting recruitment[430]. Currently, three RCTs comparing TA to resection, all for patients with CRLM ≤ 3cm, are registered: i) The COLLISION Trial (NCT03088150), a Netherland-based multi-centre phase III single-blind two-arm trial aiming to randomise 618 patients (primary endpoint: 5-year OS, start 2017)[431], ii) the NEW-COMET trial (NCT05129787), a Norway-based multi-centre double-blinded trial aiming to randomise 230 patients (primary endpoint: local tumour progression at 12 months, start 2021, iii) the HELARC Trial (NCT02886104), a Chinese open-label trial aiming to randomise 548 patients (primary endpoint: 3-year OS, start 2016)[432]. No results from these trials have yet been published as of March 2023.

Based on the overall conflicting outcomes, most guidelines on the management of CRLM refrain from making clear statements regarding the use of TA as a valid alternative to resection, stating the lack of data from RCT and concerns on the comparability of results from the available literature as main reasons. The latest National Institute for Health and Care Excellence (NICE) guideline states that "The committee had concerns about comparability of groups and selection bias influencing outcomes"[433,434]. Following these arguments, TA is still mainly performed for unresectable disease or in patients who are not surgical candidates in most centres worldwide.

2.3 Microwave versus radiofrequency ablation

Most available literature directly comparing RFA to MWA in clinical series are published for the treatment of HCC, claiming equal efficacy and OS after RFA as compared to MWA, with tendency for lower LR and RFS after MWA[435,436]. For CRLM, only few studies are currently available directly comparing outcomes after MWA versus RFA, proposing similar trends. Correa-Gallego et al.[437] and Takahashi et al.[237] reported lower LR after MWA as compared RFA (6% versus 20% and 10% versus 20%), similar complication rates (27% versus 24% and 8% versus 10%), and significantly shorter ablation times favouring MWA. Several studies including a large Chinese series confirmed similar complications rates between both ablation modalities[438,439], while others showed higher rates of biliary complications in peribiliary lesions after MWA[241]. Technical success and LR are reported varyingly, with some authors showing favourable outcomes after MWA[237,440], while others show equal results after both modalities[265,439,441]. Van Tilborg et al. reported no differences in LR and OS after MWA and RFA for peribilary and perivascular CRLM, in a series of 243 patients with 774 lesions[241]. Others confirmed similar OS rates after MWA and RFA[437,441]. The only available RCT comparing MWA to RFA showed similar short-to-long diameter ratio of ablation zones (primary endpoint) with larger ablation zones created with MWA, and similar technical success, LR and complication rates in CRLM of 1.5 to 4cm[442].

In summary, similar complication rates, similar to lower LR, longer RFS and DFS, and equal or higher OS are described after MWA as opposed to RFA for CRLM in the current literature. This was confirmed in a systematic review of outcomes after TA, describing lower median LR rates of 4.5% (1 to 24%) and 14% (10 to 37%), longer DFS rates, and longer 5-year OS rates of 55% (52 to 58%) and 43% (14 to 56%) after MWA and RFA[334].

2.4 "Free-hand" versus stereotactic instrument guidance

An augmentation in the precision of targeting intrahepatic lesions, through accurate planning of targeting trajectories and stereotactic positioning of the ablation antenna, was suggested when using stereotactic navigation technology. Through enhanced targeting accuracy, an increase in technical success and local tumour control is sought, but evidence that one leads to the other was missing. We have therefore conducted a systematic review and meta-analysis aiming to summarise the available literature on stereotactic or robotic guidance for TA of liver tumours and quantify differences in procedural and clinical outcomes when using this technology as opposed to traditional "free-hand" US or CT guidance[309] (see also chapter 1.4.1). Of the 34 included studies, nine were comparative works, including two randomized controlled studies[262,288,289,443–448]. Six reported on MWA, and three on both RFA and MWA as the TA techniques. Regarding targeting accuracy, three of 5 studies showed a significant enhancement when using stereotactic techniques[288,289,446], including the RCT reporting reduced mean targeting errors specifically for out-of-plane trajectories (5.9 versus 10.1 mm). The number of antenna readjustments were significantly reduced in all three studies reporting on this

endpoint[288,289,443], including both RCT's. Contradicting results were reported for procedural efficiency outcomes, including total procedure duration, time for ablation probe positioning and total radiation doses. The primary technique efficacy (i.e. tumours successfully eradicated following the initial procedure) was significantly enhanced after stereotactic versus free-hand TA in 6 studies included for meta-analysis, with an OR of 1.94 (CI 1.2 to 3.2, non-significant between-study heterogeneity and risk of publication bias) (Figure 19). Four PS-matched studies showed similar safety and efficacy outcomes when applying stereotactic TA for DLM versus CT-visible lesions[449], a subphrenic versus non-dome locations[283], a subcardiac versus other location[450], and in octogenerians versus younger patients[451].

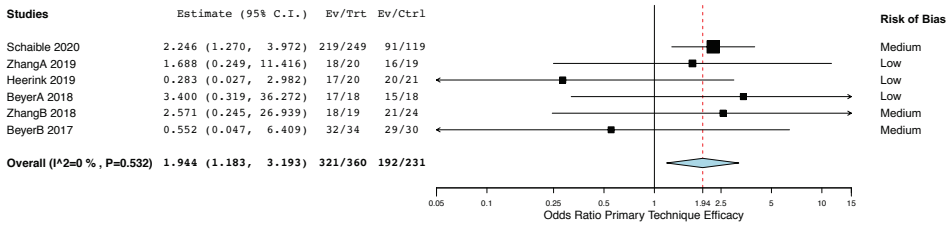

Figure 19. Pooled odds ratio of primary efficacy after stereotactic (OR > 1) versus free-hand (OR < 1) thermal ablation of malignant liver lesions. Reprinted with permission from[309] (non-adapted material, Creative Commons Attribution 4.0 International Public License, https://creativecommons.org/licenses/by/4.0/)

Importantly, the reporting of varying definitions of technique efficacy and LR severely limited comparability among studies, highlighting the need for further standardisation of follow-up definitions. Even though standardised terminology and reporting of outcomes definitions after image-guided ablation were proposed, these definitions leave large gaps for author-dependent interpretation and should be revised[335].

3 Research hypotheses and aims

Hypothesis 1: TA is non-inferior to surgical resection in terms of OS for the treatment of patients with *potentially resectable,* small (< 3cm) CRLM, and is superior in terms of safety (treatment-associated morbidity), LOS and healthcare-related costs, specifically when applying high-level technology for SMWA (Study I, III and IV)

Aim 1: Generate high-quality evidence toward the oncological validity of TA as a low-morbidity, curative-intent treatment alternative to surgical resection for patients with potentially resectable CRLM, by performing population-based analyses (Study I) and conducting a prospective multi-centre cohort trial (Study III and IV)

Hypothesis 2: The implementation of innovative computer-based algorithms allows refined analyses on the evaluation of treatment success after SMWA, permitting enhanced predictability of local tumour control after SMWA of CRLM (Study II)

Aim 2: Acquire detailed knowledge on the value of margin assessment on LR after TA, by developing (Study A, not included in thesis) and including (Study II) a novel algorithm for 3D QAM evaluation into analyses of LR after SMWA for CRLM

4 Methods

4.1 Study design and populations

4.1.1 Population-based registry study

Study I was a retrospective comparative analysis of perioperative outcomes and OS in patients that underwent TA or surgical resection for CRLM ≤ 3cm, using population-based data from a Swedish nationwide patient registry. The SweLiv database is a prospectively maintained registry containing data on patients treated for CRLM, and was described to cover 96% of all patients diagnosed with CRLM in Sweden[452]. Data on patients that underwent either MWA or surgical resection as a first intervention for CRLM between 2013 and 2016 were extracted from the SweLiv registry, including treatment-related information and baseline patient and tumour characteristics. This was complemented by data on the CRC primary tumour extracted from the Swedish Colorectal Cancer Registry, and data on patient comorbidities extracted from the National Patient Registry, for the respective patients. In general, surgical resection with or without neoadjuvant chemotherapy was offered as the treatment of choice for patients with resectable CRLM ≤ 3cm, and TA indicated for patients with non-resectable CRLM or in patients with contraindications to surgery due to comorbidities. The treatment access (open, laparoscopic or percutaneous for TA) was chosen as per the local treatment guidelines and by choice of the treating physician. OS after TA and surgical resection was compared as the primary endpoint, using PS analyses to adjust for factors known to influence the choice of treatment (MWA versus resection), in an attempt to minimise selection bias (see chapter 4.2). Univariable and multivariable survival analysis including the type of treatment and factors known to affect OS in patients with CRLM were conducted.

4.1.2 The MAVERRIC study

Studies II, III and IV are analyses and sub-analyses from the "Microwave Ablation VErsus Resection for Resectable Colorectal liver metastases" (MAVERRIC) trial (NCT0264218). The MAVERRIC trial is a European collaborative research project designed by an international study group with members from Stockholm Sweden, Bern Switzerland and Groningen Netherlands. It is a multi-centre prospective cohort study aiming to investigate whether TA is non-inferior to surgical resection in terms of oncological outcomes for patients with *potentially resectable* CRLM. The study was conducted at three European centres: i) Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden, ii) Inselspital University Hospital of Bern, Switzerland, and iii) University Medical Center Groningen, Netherlands. Inclusion criteria were patients with i) a maximum of 5 CRLM with a maximum tumour diameter of 3cm, both eligible to surgical resection only *and* SMWA only, as evaluated by the local MDT board, ii) age ≥ 18 years, and iii) legally allowed to give written informed consent. Exclusion criteria were patients with i) previous TA or more than two previous resections for CRLM, and ii) non-pulmonary extrahepatic metastases from CRC. All patients qualifying for study inclusion were recruited and gave written informed

consent for deliberate treatment with SMWA as opposed to surgical resection for their CRLM (study cohort). Outcomes from patients from the study cohort were compared to outcomes from patients that underwent treatment with the gold-standard surgical resection for their CRLM in the same time period, extracted from the SweLiv[452] population-based Swedish nationwide database (control cohort). The primary endpoint of the study was OS at 3 years (Study IV), secondary endpoints included detailed analyses on LR (Study II), subgroup analyses including healthcare-related costs (Study III) and long-term OS at 5 and 10 years. Figure 20 illustrates the MAVERRIC trial design.

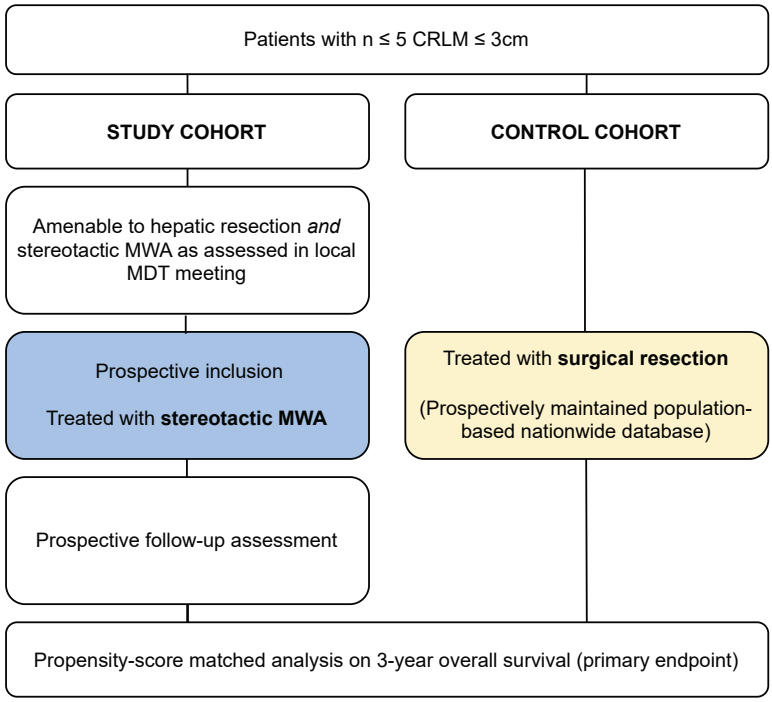

Figure 20. Flowchart of the MAVERRIC study trial design

The SMWA procedures in patients from the study cohort were performed as per the local treatment protocols in the respective centres, including the type of applied MWA device (Acculis (Angiodynamics, Latham, NY USA), Amica (HS Hospital service S.P.A, Roma, Italy) or Emprint (Covidien, Minneapolis, USA) systems), and the type of stereotactic navigation device (CAS-ONE system (Cascination AG, Bern, Switzerland) or the Needle Positioning system (NPS; DEMCON Advanced Mechatronics, Enschede, the Netherlands)). Specific workflows of respective SMWA procedures in all 3 centres were documented in detail in previous publications [252,307,453] (see also Figure 15 chapter 1.4.1). This included an initial CE-CT planning scan, an intermediate control scan for verification of the ablation antenna position, and a post-ablation verification CE-CT scan if feasible with regard to dosing limitations of intravenous contrast-agent. Clinical and radiological follow-up were

performed as per the local protocols, including clinical consultations and radiological imaging (CT or MRI imaging) at 3, 6, 12 and 36 months. All data captured for the MAVERRIC trial were entered into a password-secured RedCap database. Figure 21 illustrates the schedule of prospective data assessment including primary and secondary endpoints.

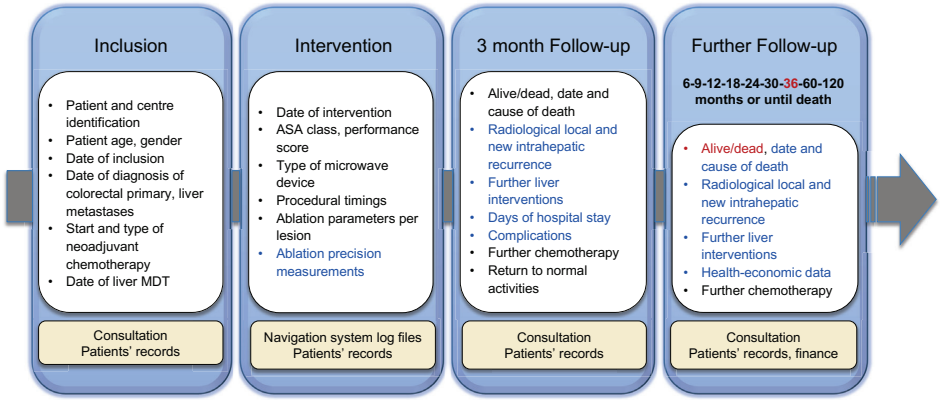

Figure 21. Workflow of data assessment in the MAVERRIC trial. Grey: data assessed, green: data assessment source, red: primary endpoint, blue: secondary endpoints

4.1.2.1 Study II

Secondary endpoint analyses within the MAVERRIC trial consisted of detailed analyses on factors affecting local tumour control after SMWA treatment for CRLM, integrating a novel algorithm for QAM assessment. A software algorithm for volumetric QAM calculation, including a novel metric for the calculation of QAM in subcapsular positions, was developed and published separately (Study A, see chapter 1.4.2)[323]. The validity of this algorithm as a precision tool for quantitative assessment of technical success, and as such as a predictor of LR after SMWA, was evaluated in Study II. From the MAVERRIC database, the CRLM treated with SMWA that had i) available pre- and immediate post-ablation CE-CT scans, ii) a clear demarcation of the CRLM on the pre-ablation CE-CT, and iii) accurate co-registration of pre- and post-ablation CE-CT scans, were included in this analysis. In the selected CRLM, tumour volumes and created ablation volumes were retrospectively segmented on pre- and post-ablation CE-CT scans, respectively, using a commercially available semi-automated segmentation software (Amira 6.3, ThermoFisher Scientific, USA). From these segmented volumes, 3D QAM defined as the distribution of Euclidean surface distances between the tumour and the ablation surface boundaries were calculated (see Figure 17). The optimal definition of the 3D-QAM output (as a continuous variable or as a categorical variable with its optimal cut-off point) were drawn from receiver operating curve (ROC)-analyses. The influence of various 3D-QAM definitions on the occurrence of LR within 1 year of SMWA, were investigated in multivariable analyses adjusting for factors known to affect LR treatment from previous studies. LR was defined as the appearance of viable tumour foci at the edge of the ablation volume after documented initial complete ablation[335].

4.1.2.2 Study III

Further secondary endpoint analyses included the comparison of healthcare-associated costs after SMWA versus resection of CRLM (Study III). This was investigated in the Swedish sub-cohort of the MAVERRIC trial, due to the specific pattern of study inclusion in this patient subgroup. At the local MDT in Stockholm, patients with CRLM were considered for inclusion into the MAVERRIC study only every *odd* calendar week, while on *even* calendar weeks, patients were treated as per the gold standard surgical resection. This was chosen as to maintain a manageable workflow and avoid delays in SMWA treatments, which is performed only at one centre in the greater Stockholm area. This particular inclusion pattern led to the formation of two "quasi-randomised" patient cohorts, both amenable to SMWA *and* surgical resection, treated with either SMWA (included into the MAVERRIC study) or surgical resection, during the same inclusion period. Surgical resection was performed as per the local standards at the Stockholm tertiary centre for HPB surgery (Karolinska Hospital Huddinge), applying a MI laparoscopic approach whenever feasible. Baseline healthcare consumption 1 year prior MDT discussion for the index treatment was assessed, and healthcare consumption and healthcare-related costs, including for the index treatment and 2 years onwards, were extracted (Figure 23). Diagnosis-Related Group (DRG) and Cost Per Patient (CPP) measures were used for calculation of inpatient admission and outpatient visit costs, and hospital economists were consulted for calculation of other costs. Peri-operative and survival outcomes at 2 years after the index treatment were extracted, and multivariable analyses on factors influencing OS, including the type of treatment, conducted.

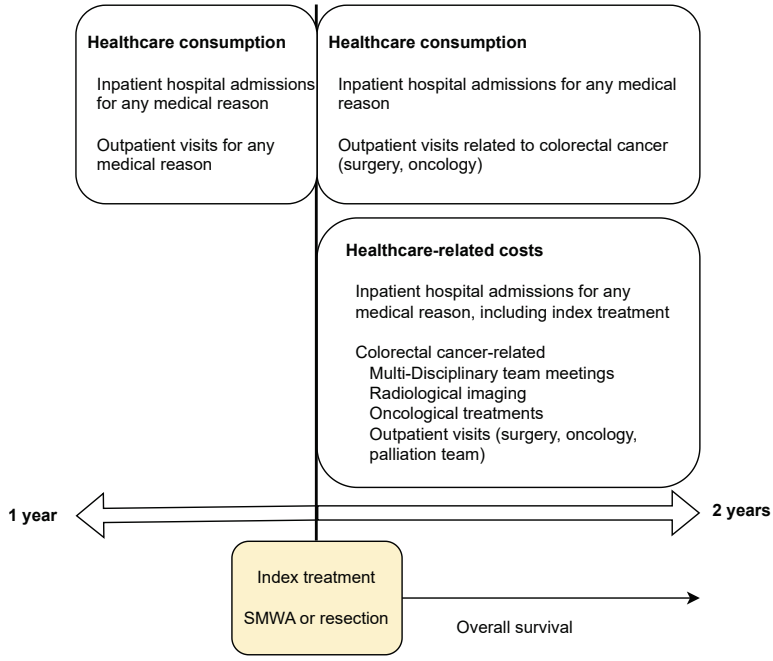

Figure 23. Data assessment including factors related to healthcare consumption and costs prior and after index treatment

4.1.2.3 Study IV

The primary study endpoint of OS at 3 years after index treatment (SMWA in the study cohort, surgical resection in the control cohort) was analysed in Study IV. The control cohort was extracted from the prospectively maintained Swedish nationwide patient registry (SweLiv registry), containing detailed data on the treatment and outcomes of all patients treated for liver tumours in Sweden[452]. Clinical, treatment-related and outcome data of patients treated with surgical resection for a maximum of 5 CRLM ≤ 3cm within the same period as the inclusion period for the MAVERRIC trial were extracted from SweLiv. Additional information on the primary CRC tumour and on patient comorbidities were extracted from two other Swedish nationwide patient registries (National Patient Register and Swedish colorectal cancer registry) for the corresponding patients[454,455]. Treatment-related complications were reported according to the Clavien-Dindo classification[456], and patient comorbidities at the time of index treatment were calculated according to the Charlson comorbidity index (CCI)[457]. OS in the study and control cohorts was compared using PS analysis for the creation of two comparable cohorts in terms of baseline characteristics and to address confounding by indication, including factors known to affect OS in patients treated for CRLM.

4.2 Statistical considerations

For the MAVERRIC trial, a sample size calculation was performed based on a computer-simulated random sampling method. A liver-specific international database (The LiverMet Survey[458]), containing prospectively collected data from over 25'000 patients from 69 countries that underwent resection for CRLM, was used. A subset of patients that underwent a first resection of a single CRLM smaller than 3cm (corresponding to an assumed "best case" scenario regarding OS) were extracted from this database (n = 1387), and OS curves after CRLM resection were generated using the Kaplan-Meier method. From this dataset, a random sample of 100 patients were selected and their survival curves compared to the entire subset of 1387 patients, at a non-inferiority level of 10% below the lower-bound 90% CI (statistical power of 90%) at 3 years. This yielded a sample size of 92 patients, corresponding to a probability above 90% to show non-inferiority with the new treatment modality (Figure 22). To allow potential dropouts of included patients, a sample size of 100 patients was aimed to be included in the study group.

Statistical analyses in Study I, III and IV were performed using STATA/IC version 16.0 (StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA), and in Study II using R (R Core Team, 2019) and RStudio (RStudio Inc., USA). The main statistical methodology applied in Studies I, III and IV were time-to-event analyses, including univariable and multivariable models to study survival probabilities and the effect of different treatment groups on the hazard of death. OS curves were generated using the Kaplan-Meier method, initially published by Böhmer in German in 1912[459] and by Kaplan and Meier in English in 1958[460]. This method is a non-parametric statistic estimating stepwise survivor functions

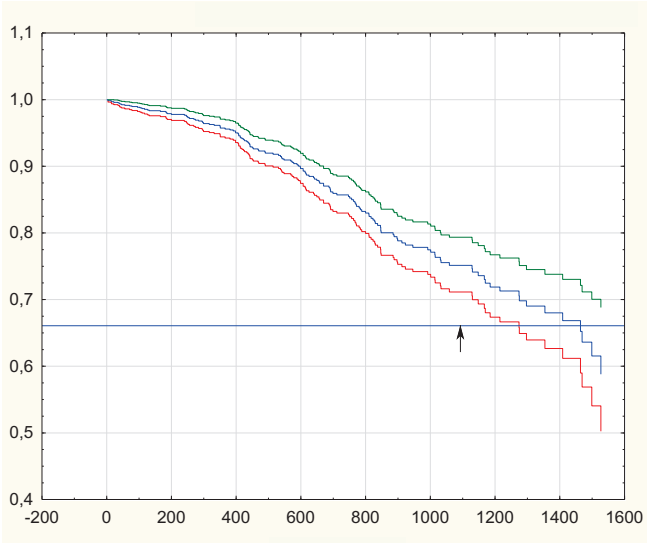

Figure 22: MAVERRIC trial sample size calculation. The relative overall survival probability (y-axis) over time in days (x-axis) of 1387 patients after resection of 1 CRLM ≤ 3cm, extracted from the LiverMet survey database, is shown (blue) with a 90% confidence interval (green and red lines). Straight blue line: cut-off 10% below the lower 90% confidence interval at 3 years (arrow). Of 100 randomly selected patients, 92 had a survival probability above the selected cut-off point

based on the interval-specific survival status at each event time, with interval size decreased toward zero and assuming that events precede censorings. It allows to estimate the probability of survival of a given patient relative to a "surviving" population, at a certain time point (e.g. at 3 years) after a certain event in time (*starting point*) and as opposed to death or censoring (*ending point*). In Study I, the starting point was defined as the *date of CRLM diagnosis*, while in Studies III and IV, the *date of index treatment* (SMWA or resection) was chosen. The former definition allowed to depict the true oncological survival from the time of diagnosis, including potential neoadjuvant chemotherapy treatments. The latter definition allowed to exclude potential *immortal time* bias between CRLM diagnosis and treatment, eventually leading to bias in favour of the *treated* (i.e. the SMWA) group[373]. A 24-hour interval (time in days) was applied as the time interval, however leaving a certain bias due to the presence of ties (between death and censoring), while the Kaplan-Meier method was designed for use on a continuous and not discrete scale. *Time of death by any diagnosis* was chosen as the ending point, if censoring did not occur first. To this regard, a main methodological strength of the MAVERRIC study was the comprehensive prospective patient follow-up until the primary endpoint (3-year OS) for all patients, with minimal censoring due to loss to follow-up. This allowed to depict true survival at the defined follow-up as opposed to extrapolated estimations of survival. The Log rank test and the Wilcoxon (Breslow) test were applied for comparison of survival functions. The threshold for statistical significance was set to alpha = 0.05 in all analyses.

All studies were (semi-)observational in their design with respective high probability of significant systematic differences in i) baseline characteristics other than the type of

CRLM treatment (SMWA versus resection) affecting OS in patients treated for CRLM, and ii) characteristics affecting the choice treatment (see also chapter 6.3). Aiming to minimise bias due to study design and increase internal validity of results, different statistical methods were applied to adjust for confounding. In Studies I and IV, PS-based analyses were performed, a method first described by Rosenbaum and Rubin in 1983[461]. In brief, the *true* PS balances the distribution of observed baseline characteristics (confounders to the true treatment effect) across two treatment groups, which will thus become similar in both cohorts and independent of treatment assignment, conditional on the PS. In other words, the *true* PS represents the probability of a certain treatment to be assigned to a certain patient independent of observed baseline characteristics. PS analysis was chosen as the primary methodology to address bias in Studies I and IV, since, as opposed to the more common Cox or Poisson regression adjustment, it allows i) an estimation on marginal effects at a population level, ii) an easier verification of the adequacy in the model specification, iii) a transparent analysis of the overlap in the distribution of covariates across cohorts, and iv) a separation of the model design and the outcome analysis, mimicking the study design and related advantages of an RCT[462]. The crucial and critical assumption of PS analysis (alike regression analysis) is the condition of "no unmeasured confounders". We selected baseline characteristics known to influence the choice of treatment (Study I) and affect OS in patients treated for CRLM (see also chapters 1.2.4 and 2.1, Table 2)(Study IV), which were available in our study populations. Since the *true* PS is not known in observational studies (as opposed to RCT's), it is estimated by regressing the treatment type on observed baseline characteristics[462]. In Study I, the PS was estimated based on a probit model using the "psmatch2"-command. In Study IV, a logistic regression analysis was applied and the adequacy of the model specification validated using standard techniques[463]. Nearest-neighbour (i.e. greedy) matching was performed in both studies, limiting controls to a maximum of 2 and using a caliper of 0.2 of the standard deviation of the logit of the propensity score, to minimize the mean squared error of the estimated treatment effect, in Study IV[464,465]. Standardized differences (StD) of baseline characteristics across cohorts, and side-by-side boxplots, were applied for balance diagnostics after PS matching. StD correspond to the difference in means in units of pooled standard deviations, and, unlike p-values, are independent of sample size. A StD of < 0.1 was considered as an adequate balance[466]. Following the protocol proposed by P. C. Austin for the "conduct and reporting of PS methods on time-to-event outcomes using observational data"[467] in Study IV, survival probabilities using Kaplan-Meier curves were compared using a stratified Log rank test, and the treatment effect (hazard ratio (HR) with 95% CI) estimated using univariable Cox regression in the matched sample. To investigate a potential new selection bias introduced by the PS matching itself, survival probabilities were also compared between matched patients and patients that remained non-matched in Studies I and IV.

Additionally to PS analyses, multivariable Cox proportional hazard models were applied, to i) adjust for confounders (baseline characteristics known to affect survival in patients treated for CRLM) when estimating the relative treatment effect of SMWA versus resection on OS (HR with 95% CI) in Study III, and ii) as sensitivity analyses validating

comparative results obtained from PS analyses, and estimating relative effects (HR with 95% CI) of other covariates on OS, in Studies I and IV. The assumption of proportionality in the hazard ratios over time was confirmed by testing time-dependency of Schoenfeld residuals and the effect of adding a time-dependent interaction term to multivariable Cox models.

In Study II, we performed multivariable analyses to investigate the effect of different definitions of 3D-QAM on LR within one year after SMWA, while adjusting for characteristics known (and available to us) to affect LR (see Table 2). While analysis was done on a *per-tumour* basis, some baseline characteristics (e.g. chemotherapy, CEA-levels, KRAS mutational status) were *patient-specific*, which violates the assumption of independence in observations made in classic regression analysis, when including multiple tumours treated in the same patient. To statistically account for these intra-class correlations, we applied repeated-measure analyses using generalised estimated equations (GEE), a technique introduced by Liang and Zeger in 1986[468]. As opposed to random effect (mixed) models, GEE or *population-average models* were described as less prone to biased inference due to unverifiable assumptions on the underlying data distribution, since approximation to the true underlying model can be defined explicitly[469]. The use of robust estimators of the covariance allows unbiased standard errors and a larger degree of freedom in model specification as opposed to mixed models. The assumptions related to GEE analyses in Study II were confirmed by testing independence of between-cluster observations and adequate sample size for asymptotic inference. ROC analysis was applied to identify the optimal 3D-QAM definition, with an area-under-the-ROC-curve (AUC) of > 0.7 considered as an acceptable test performance.

4.3 Ethical considerations

Study I was a population-based registry study, using data stored prospectively and anonymised in Swedish nationwide registries. No additional risks to the specific patients arose due to the conducted data analyses. Approval by the Regional Ethical Review Board in Stockholm was obtained (Dnr: 2016/2048e31/1).

In the MAVERRIC study, patients with CRLM eligible for both surgery and TA were deliberately assigned SMWA treatment. While the overall available data is inconclusive whether oncological outcomes after TA are comparable to surgery, several more recent studies meticulously reducing bias in their comparative study design suggested likewise. TA was further shown to be favourable in terms of treatment-related morbidity and enhanced treatment opportunities in case of disease progression. TA with SMWA was shown to be safe and effective in several large clinical series[252,289]. Beyond the actual treatment decision, there were no additional study-specific risks to the participating patients, who gave written informed consent for study inclusion. Data was stored anonymised on a secured web server. The expected benefit from this study was a hope to significantly contribute to the ongoing discussions toward the most effective and

suitable treatment practice for patients with small CRLM, with respective impact on patient morbidity, time spent in medical facilities and costs. By weighting the risks against the benefits, we felt that it was ethically justified to carry out this study, which was approved by all three corresponding ethical review boards (Bern: KEK 317/15; Groningen: 2016/004; Stockholm: Dnr 2015/1453-31/4, with the addition Dnr 2020-00787 for Study III).

The limitations of any statistical inference to an assumed underlying true data distribution (see also chapter 6.3), should be kept in mind also from an ethical point of view, knowing that "All models are wrong but some are useful" (George E.P. Box)

5 Results

5.1 Study I

From a total of 1255 patients extracted from the SweLiv data registry, 528 patients were excluded due to simultaneous resection and TA (n = 116), a non-resected primary CRC tumour (n = 147), CRLM size > 3cm (n = 186), non-MWA TA (n = 44) or missing data (n = 35). A total of 727 patients (82 MWA patients, 645 resection patients) fulfilling the inclusion criteria remained eligible for analysis (baseline population).

There were statistically significant differences in baseline characteristics in this population, with patients that underwent MWA having a higher median age, American Society of Anaesthesiology (ASA) score and CCI, number of CRLM, and a right-sided primary CRC tumour, and less frequently received neoadjuvant chemotherapy, than patients that had received resection of CRLM. Also, MWA was performed more frequently in patients treated in the later versus the earlier time period. This was confirmed when applying multivariable logistic regression analysis to investigate factors affecting the choice of treatment, where WHO performance status was lower, ASA class and number of CRLM were higher and neoadjuvant chemotherapy was less frequent in patients treated with MWA as opposed to resected patients. All baseline characteristics except the primary CRC tumour nodal stage had a StD > 0.1. PS matching yielded two balanced groups (70 MWA patients, 201 resection patients) with regard to PS distribution and baseline characteristics across groups, with an average StD in all baseline characteristics dropping from 0.309 in the baseline population to 0.097 after PS matching (Figure 24).

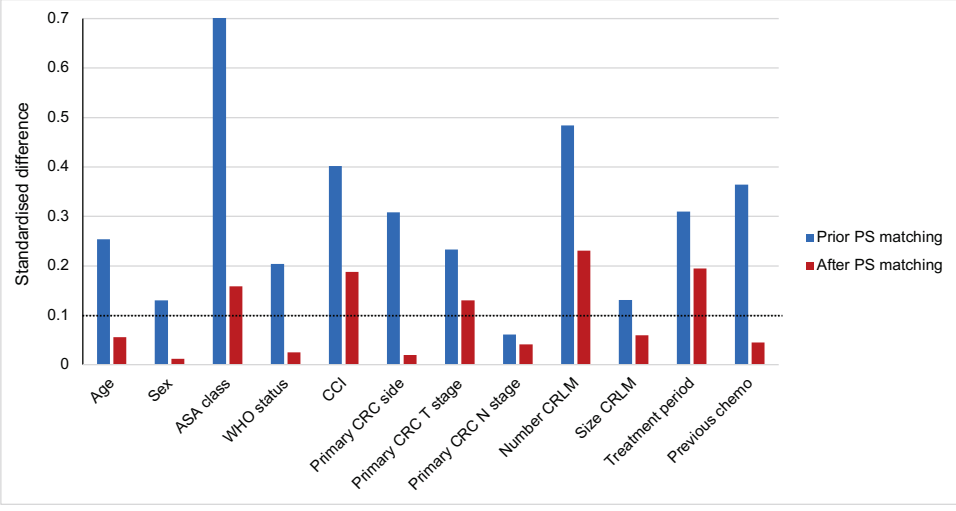

Figure 24. Standardised differences in baseline characteristics across patients that underwent microwave ablation versus resection, prior (blue) and after (red) propensity score matching. Dotted black line: Threshold of 0.1

Median overall follow-up time was 24 months (IQR 15 to 36 months). In the baseline population, median OS was 43 months (95% CI 32 to 55 months) after MWA versus 55 months (95% CI 51 to 58 months) after resection, with 3-year OS probabilities of 69% versus 76% ($p < 0.01$). In the PS matched population, median OS was 48 months (CI 40 to 56 months) after MWA versus 55 months (95% CI 49 to 61 months) after surgical resection, with 3-year OS probabilities of 76% (95% CI 59% to 86%) versus 76% (95% CI 68% to 83%) ($p = 0.253$) (Figure 24). Multivariable Cox regression analysis in the baseline population confirmed that the treatment type did not affect OS after MWA versus resection (HR 1.43 (95% CI 0.77 to 2.65, $p = 0.255$), with age, nodal status of the primary CRC tumour and number and size of CRLM as statistically significant factors affecting OS.

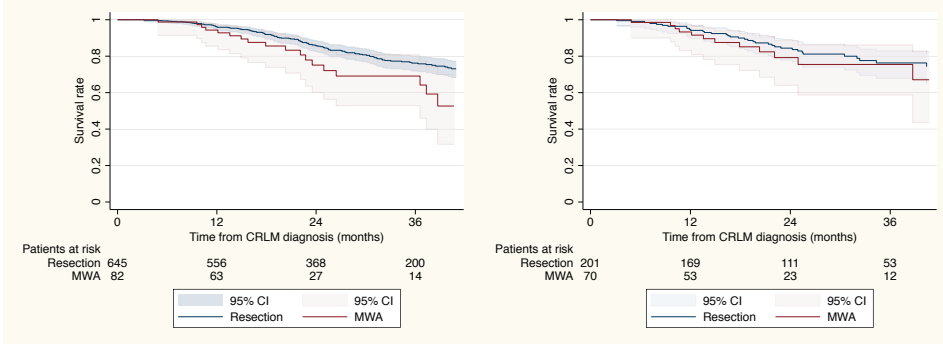

Figure 24. Relative overall survival probabilities after microwave ablation (red) versus surgical resection (blue) since diagnosis of CRLM, prior (left) and after (right) propensity score-matching

In patients that underwent MWA, there were statistically significant differences in baseline characteristics in the patient populations that were included for PS analysis versus the populations that remained non-matched (n = 12), the latter having older age, higher ASA class, lower WHO performance status and higher CCI score. Accordingly, 3-year OS was shorter in this group (44% versus 76%, $p < 0.03$). In patients that underwent resection, there was no statistically significant difference in OS when comparing the patient populations that were included for PS analysis versus the populations that remained non-matched (n = 444), with a 3-year OS of 76% versus 76% ($p = 0.875$).

Median LOS in the MWA versus resection group was 1 day (IQR 1 to 2 days) and 7 (IQR 5 to 9 days), respectively ($p < 0.01$). Severe complications (Clavien-Dindo ≥ III) within 30 days of treatment occurred in 5 (7%) versus 33 (16%) patients that underwent MWA versus resection ($p = 0.046$). Twenty-six (37%) patients in the MWA group underwent one to five further interventions, of which 69% were further TA and 31% were further resections. Thirty-one (15%) patients in the resection group had one to three further interventions, of which 68% were further resections and 32% were further TA.

5.2 Study II

A total of 65 CRLM tumours treated with SMWA in 47 patients were included for analysis. Median tumour diameter was 13mm (IQR 10 to 20 mm), with two tumours larger than 30 mm due to tumour growth between patient inclusion in the MAVERRIC study and SMWA treatment (34mm and 41mm). Baseline patient, CRLM and primary CRC tumour characteristics are summarised in Table 4.

Patient characteristics	
Female sex, male sex	15 (32), 32 (68)
Age (years)	69 (62 to 74)
Neoadjuvant chemotherapy	16 (34)
CEA level	3.6 (1.9 to 7.8)
Number of treated CRLM	2 (1 to 2)
Primary CRC tumour characteristics	
Right-sided, left-sided location	50 (77), 13 (20)
N0, N1-2	18 (38), 29 (62)
KRAS mutated, wild type	22 (47), 21 (45)
CRLM characteristics	
Synchronous, metachronous, recurrence after resection	18 (38), 23 (49), 6 (13)
Left liver, right liver, caudate lobe	13 (20), 50 (77), 2 (3)
Subcapsular (<5mm from liver capsule)	30 (46)
Perivascular (< 5mm from >3mm intrahepatic vessel)	16 (25)
Maximal diameter (mm)	13 (10 to 20)

Table 4. Baseline patient (n =47) and tumour (n = 65) characteristics in. Numbers (percentages) or medians (IQR) are shown

The median ablation time per tumour was 4 min (IQR 3 to 8 min), with a median power of 100 Watts (IQR 80 to 140 Watts). The median number of ablation antenna positionings was 1 (IQR 1 to 5), with a median procedural radiation dose (dose length product) of 1.192 mGy*Cm (IQR 960 to 1.925 mGy*cm). From the direct overlay of pre- and post-procedural CE-CT images for immediate validation of treatment success, all CRLM treated with SMWA included in this analysis were judged completely ablated (the volumetric QAM evaluation was retrospectively applied in the current study and was not available at the time of SMWA treatment).

Ten of 65 (15%) included CRLM developed LR within one year of SMWA treatment. There were no statistically significant differences in ASR rates between the three centres (Fisher's exact p = 0.356). The median MAM was -2.4 mm (IQR -3.2 to -1.4 mm) versus 0.0 mm (-0.9 to 2.4 mm) ($p < 0.01$) and the 3D-QAM < 0mm was 11.5% (IQR 1.9 to 18.9%) versus 0.0 (0.0 to 0.9%) ($p < 0.01$) in patients who developed ASR versus patients who did not develop ASR. There was no ASR in tumours with a 100% tumour coverage (100% 3D-QAM) of ≥ 2 mm and a 90% 3D-QAM of ≥ 3 mm. Figure 25 illustrates an example of the 3D-QAM generation and output computed in a CRLM located in liver segment V treated with SMWA included for analysis.

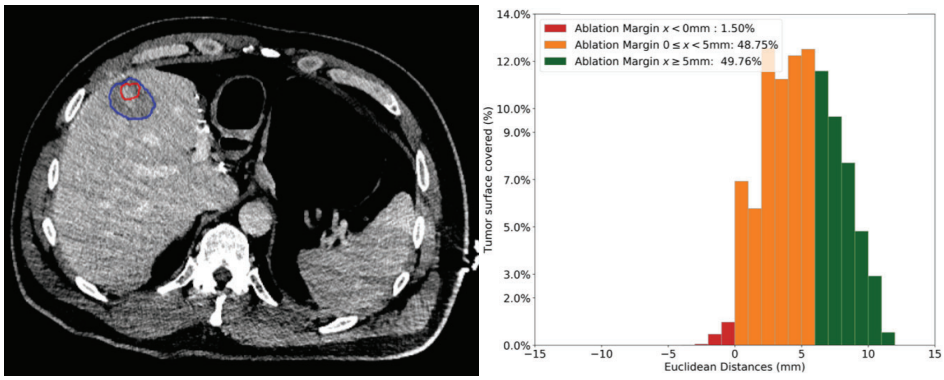

Figure 25. Example case of quantitative ablation margins obtained in a colorectal cancer liver metastasis treated with stereotactic microwave ablation. Left: outlined segmentations of tumour (red) and ablation (blue) volumes. Right: relative distributions of ablation margin bins (percentage of tumour surface covered with ablation volume), coloured in green (> 5mm), orange (0 to 5mm) or red (< 0mm)

The ROC analyses investigating the optimal diagnostic ability of the 3D-QAM output yielded the highest AUC (0.77) for a 3D-QAM defined as the percentage of tumour coverage by at least 1 mm with a cut-off value at 23%. The MAM defined as a continuous variable yielded an AUC of 0.82 (Figure 26).

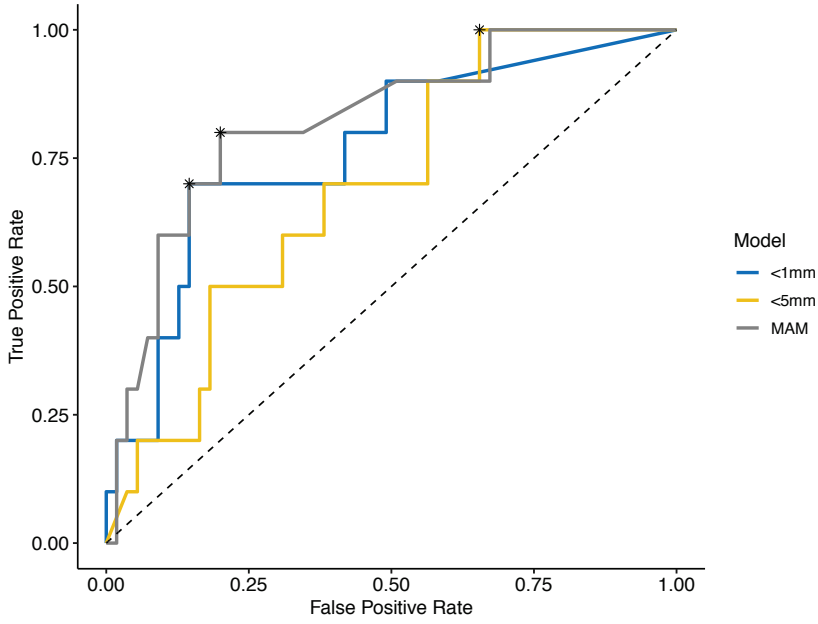

Figure 26. Receiver operating curves investigating the diagnostic ability of quantitative ablation margins. Blue: 3D- QAM defined as the percentage of ablation margins below 1mm. Yellow: 3D- QAM defined as the percentage of ablation margins below 5mm. Grey: QAM defined as the minimal ablation margin (MAM). The asterix' mark optimal cut-off points

Logistic regression models using GEE were created, investigating the effect of various 3D-QAM definitions on LR after SMWA. The baseline model without 3D-QAM yielded the maximal tumour diameter (OR 1.11, 95% CI 1.05 to 1.18) and the KRAS mutational status (OR 0.29, 95% CI 0.09 to 0.97) as significant factors affecting LR. When adding 3D-QAM defined as MAM or as > 23% of 3D-QAM < 1 mm, this became the most important predictor of LR (Table 5). The odds to develop LR was on average 48% lower for every additional millimetre of MAM (Model B), and was on average 21 times larger when more than 23% of the tumour surface was covered by a margin < 1mm.

Covariables	Baseline Model A		Model B		Model C	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Neoadjuvant chemo (y/n)	1.22 (0.33, 4.54)	0.77	4.14 (0.52, 33.18)	0.18	1.97 (0.35, 11.04)	0.44
Previous resection (y/n)	0.12 (0.01, 1.29)	0.08	0.79 (0.01, 74.51)	0.75	0.79 (0.01, 74.51)	0.92
CEA level*	1.89 (0.52, 6.85)	0.33	1.94 (0.15, 14.45)	0.54	1.49 (0.15, 14.45)	0.73
KRAS mutated (y/n)	0.29 (0.09, 0.97)	0.04	0.47 (0.07, 3.4)	0.45	0.62 (0.08, 4.61)	0.64
Perivascular CRLM (y/n)	1.01 (1, 1.02)	0.19	1.02 (0.98, 1.25)	0.86	1.01 (0.87, 1.17)	0.89
CRLM diameter*	1.11 (1.05, 1.18)	< 0.01	1.10 (0.98, 1.25)	0.12	1.13 (1.01, 1.27)	0.04
3D-QAM	--	--	0.52 (0.29, 0.95)	0.03	21.67 (2.84 165.21)	< 0.01

Table 5. Multivariable analysis using generalised estimating equations. Model A: Baseline model without ablation margin as covariable. Model B: Baseline model plus 3D-Quantitative ablation margin defined as the minimal ablation margin (MAM). Model C: Baseline model plus 3D-Quantitative ablation margin defined as > 23% < 1 mm; *Continuous variable

5.3 Study III

A total of 681 patients with CRLM were reviewed in 1090 MDT sessions at the joint regional liver MDT from the greater Stockholm area between December 2015 and November 2018. Of these, 105 fulfilled the inclusion criteria for the MAVERRIC trial (≤ 5 CRLM ≤ 3 mm, amenable to both resection *and* TA with SMWA), of which 52 were included into the trial on *even* calendar weeks and treated with SMWA, while the other 53 were not included on *odd* calendar weeks and treated with surgical resection (Figure 27). Baseline characteristics were similar in both groups, including comorbidity indexes, performance status, tumour burden, rate of *liver first* approaches and health care consumption one year prior index treatment (SMWA or resection), with the exception of a higher rate of previous liver resections and of non-oncology related outpatient visits in the SMWA versus resection group (Table 6). In the liver resection group, the main type of resection were 51% atypical local resections, 26% segmental resections, 19% right lobectomies and 4% left lobectomies, with 23% of them performed over a laparoscopic access and 11% converted from a laparoscopic to an open access. Thirty per-cent (n = 16) of resected patients had synchronous resection of the primary CRC tumour, but none of the SMWA patients (due to logistic reasons). The rate of R0 margins in all resected specimen of 81% in the resection group was similar to the treatment efficacy rate of no tumour residue at the ablation site at 3-months of 85% in the SMWA group.

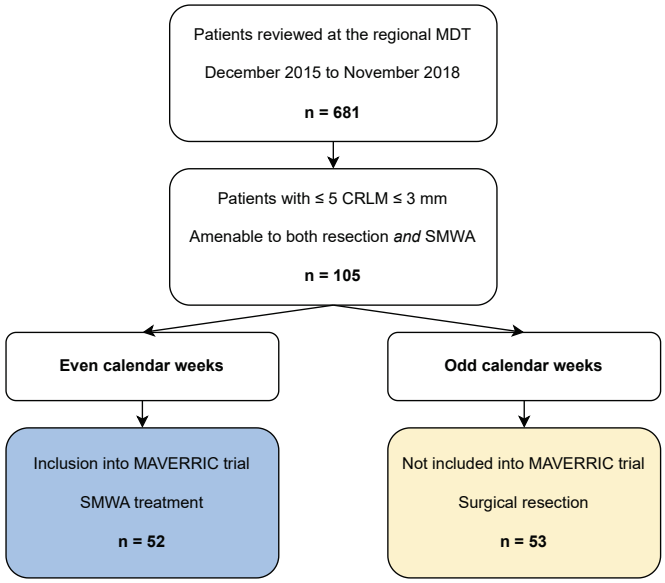

Figure 27. Flowchart of patient inclusion, resulting in a "quasi-randomised" methodological situation

Patient characteristics	SMWA	Resection	p-value
Female sex, male sex	19, 33	22, 31	0.602
Age (years)	68 (62 – 77)	66 (61 – 72)	0.396
ASA class (I, II, III, IV)	5, 26, 18, 3	12, 25, 13, 3	0.297
CCI (≤7, 8, 9, 10, ≥11)	8, 13, 15, 7, 9	10, 17 16, 5, 5	0.700
WHO performance status (0, 1, ≥2)	27, 22, 3	33, 18, 2	0.593
Previous liver resection (yes, no)	5, 47	0 53	0.027
Perioperative chemotherapy (no, neoadjuv., adjuv., both)	32, 3, 6, 11	24, 5, 7, 17	0.398
Primary tumour in situ "Liver fist" approach (yes, no)	23, 29	14, 23	0.546
Synchronous lung metastasis (yes, no)	1, 51	5, 48	0.205
Primary CRC tumour characteristics			
Tumour location (right, left)	20, 32	20, 33	0.939
T-stage (0, 1, 2, 3, 4, 5)	1, 1, 7, 30, 13, 0	1, 3, 6, 20, 20, 3	0.305
N-stage (0, ≥1, unknown)	16, 36, 0	14, 36, 3	0.703
KRAS mutation (yes, no, unknown)	22, 30, 0	9, 10, 34	0.703
Perioperative chemotherapy (no, neoadjuv., adjuv., both)	16, 19, 15, 2	13, 15, 20, 3	0.668
Resected within one year prior index treatment (yes no)	25, 27	33, 20	0.144
CRLM characteristics			
Number of treated CRLM (1, 2 to 5)	24, 28	29,24	0.380
Bilobar distribution (yes, no)	11, 41	11, 42	0.960
Size of largest tumour (mm)(mean, SD)	15, 6	15, 7	0.905
Baseline healthcare consumption			
Outpatient visits oncology related (median, IQR)	7.5 (2 - 33	7 (3 – 19)	0.602
Outpatient visits non-oncology related (median, IQR)	5 (2 – 11.5)	2 (1 – 6)	0.003
Inpatient hospital admissions (median, IQR)	1 (0 – 2)	1 (0 – 1.5)	0.520

Table 6. Baseline characteristics in patients undergoing SMWA (n = 52) or resection (n = 53) for CRLM. Absolute numbers are shown

Median LOS, rates of overall and severe complications and median number of admissions to rehabilitation centres were significantly reduced in the MWA versus resection group (1 versus 7 days, 15% versus 60%, 2% versus 25%, 0 versus 24, respectively). Severe complications remained lower when excluding the 4 out of 16 patients undergoing simultaneous resection of the CRC primary tumour who developed severe complications, of whom only one had a colon-related complication (colo-vesical fistula requiring re-operation). Liver-specific severe complications included seven cases of perihepatic collections requiring drainage and three cases of bile leaks requiring endoscopic drainage in the resection group, and none in the SMWA group. There was one mortality in each group (a case of combined liver and kidney failure after right lobectomy and local resections for bilobar CRLM, and a case of cardiac death 21 days after SMWA complicated by liver abscess fistulating into small bowel requiring surgical intervention).

Health care consumption from patient inclusion at the liver MDT and two years onwards were similar in both groups (outpatient visits and inpatient hospital admissions), except for a higher number of radiological imaging in the SMWA group. Total costs from liver MDT and two years onwards were significantly lower after SMWA versus surgical resection (median US$ 66058 (IQR 43641 – 103229) versus US$ 104374 (64125 – 144149)) ($p < 0.01$). This difference was mainly related to inpatient hospital admissions including the index treatment admission, with similar costs for outpatient visits, MDT conferences and oncological treatments (Figure 28).

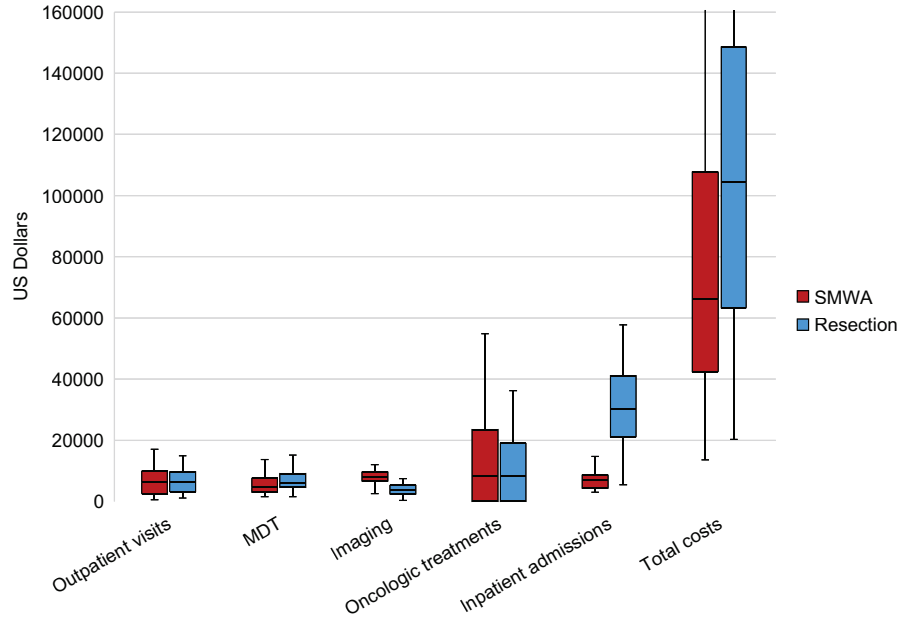

Figure 28. Distributions of costs from decision for index treatment at the MDT conference and two years onwards. Medians, interquartile ranges and extremes are shown

Median follow-up time was 46 (IQR 37 to 63) months and 48 (30 to 58) months in the SMWA versus resection groups, respectively. Liver-specific RFS at 2 years was shorter in the SMWA versus resection group (35% versus 55%, p = 0.014) (Figure 29 left). Fifty-two per-cent of patients in the SMWA group underwent further liver interventions within 2 years, of which 90% were re-ablations and 10% were resections, versus 26% in the resection group (81% re-resections, 9% ablations). DFS at 2 years was 29% versus 40% in the SMWA versus resection groups, respectively (p = 0.150) (Figure 29 right). OS at 2 years was 89% (76% to 95%) versus 79% (66% to 88%) in the SMWA versus resection groups, and estimated 3-year OS was 75% (CI 61% to 85%) versus 70% (40% to 67%) (p = 0.947 Log rank test, p = 0.831 Wilcoxon-Breslow test) (Figure 30). Multivariable regression analysis confirmed no significant effect of the type of treatment on OS (HR 1.0, CI 0.6 to 1.7), with the number of CRLM as the only covariable affecting OS (HR 2.4, CI 1.3 to 4.6).

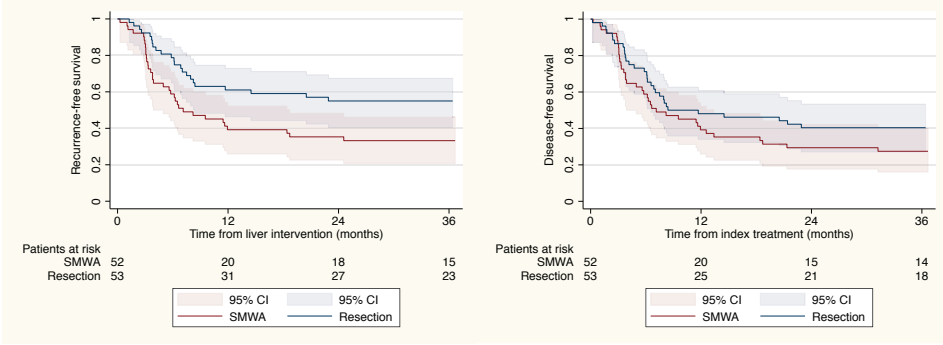

Figure 29. Liver-specific recurrence-free survival (left) and disease-free survival (right) after index treatment

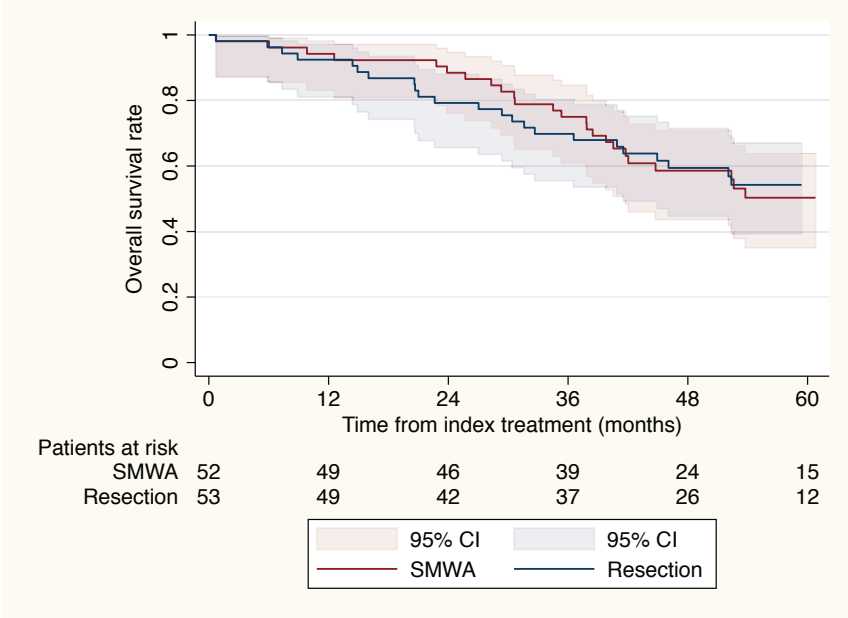

Figure 30. Relative overall survival probabilities of patients with CRLM treated with SMWA (red) versus resection (blue)

5.4 Study IV

Between December 2015 and December 2018, 108 patients were prospectively included into the MAVERRIC study. Ten patients were excluded from the final analysis due to i) unexpected origin from prostate cancer rather than from CRC (as shown in pre-SMWA biopsy) (n = 1), and ii) screening errors resulting in failure to meet inclusion criteria (n = 9), resulting in a final study cohort of 98 patients treated with SMWA. A total of 692 patients treated with resection were extracted from the SweLiv registry as the control cohort.

The designed PS model yielded an adequate balancing property of the PS and a comprehensive overlap in the range of assigned PS (i.e. common support) across treatment cohorts. PS matching yielded a matched study cohort of all 98 patients treated with SMWA, and a matched control cohort of 256 patients treated with resection, with an adequate distribution of baseline characteristics across treatment cohorts. Main baseline characteristics in the matched sample are shown in Table 7. The average StD in all covariables before matching was 0.191, and post matching 0.077 (Figure 32). Different matching strategies (e.g. allowing up to 5 matched controls or restricting to 1-to-1 matching) all yielded average StD < 0.1 across all covariables, strengthening the argument of a well-designed PS model.

Patient characteristics	SMWA	Resection	p-value
Female sex, male sex	34%, 66%	35%, 66%	0.761
Age (median, IQR)	68y (62 – 74y)	68y (61 – 74y)	0.934
ASA class (I - II, III - IV)	60%, 40%	36%, 64%	0.550
CCI (≤7, 8 - 10, ≥11)	15%, 73%, 12%	14%, 80%, 7%	0.309
Neoadjuvant chemotherapy	33%	37%	0.509
First liver intervention	84%	84%	0.978
Synchronous lung metastases	1%	6%	0.094
Primary CRC tumour characteristics			
Tumour location (right, left)	17%, 83%	15%, 85%	0.647
T-stage (0 - 2, 3 - 4)	17%, 83%	18%, 82%	0.914
N-stage (0, ≥1)	39%, 61%	42%, 58%	0.637
CRLM characteristics			
Number of treated CRLM (median, IQR)	1 (1 – 2)	1 (1 – 2)	0.754
Size of largest tumour (median, IQR)	16 (12 – 23) mm	18 (15 – 25) mm	0.156

Table 7. Baseline characteristics in matched SMWA (n = 98) and resection (n = 158) cohorts

In the matched resection cohort, 14% were major resections (> 3 adjacent liver segments *en bloc*), the rest being minor resections, and 18% were performed via a laparoscopic approach. In the SMWA cohort, technical success rate was 96%, with 6 out of 7 tumours with incomplete ablation undergoing re-ablation within 1 months, leading to a primary efficacy rate of 99%. The per-tumour LR rate within one year was 17%, with 14 of 28 tumours re-treated with SMWA, leading to a secondary efficacy rate of 92%. Seventy per-cent of CRLM with LR had concomitant new intrahepatic tumours and 17% concomitant new extrahepatic disease.

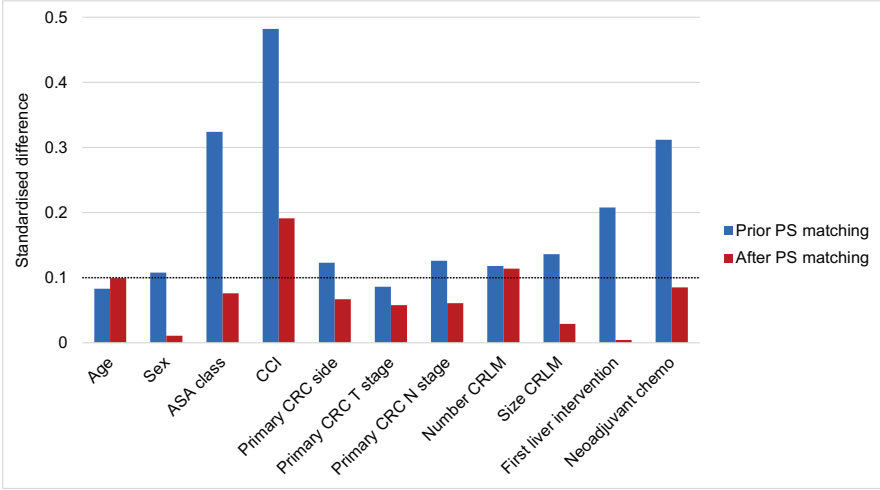

Figure 32. Standardised differences in baseline characteristics across patients that underwent SMWA versus resection, prior (blue) and after (red) propensity score matching. Dotted black line: Threshold of 0.1

Median follow-up time was 51 (IQR 38 to 61) months and 47 (36 to 64) months in the SMWA and resection cohorts. A total of 48% of patients in the SMWA cohort underwent hepatic re-interventions for any hepatic CRLM recurrences within three years, versus 27% in the resection cohort ($p < 0.01$). These were repeat TA in 85% in the SMWA and 59% in the resection cohorts. The observed 3-year OS (primary endpoint) was 78% (CI 68% to 85%) in the SMWA and 76% (69% to 82%) in the resection cohorts ($p = 0.861$) (Figure 33).

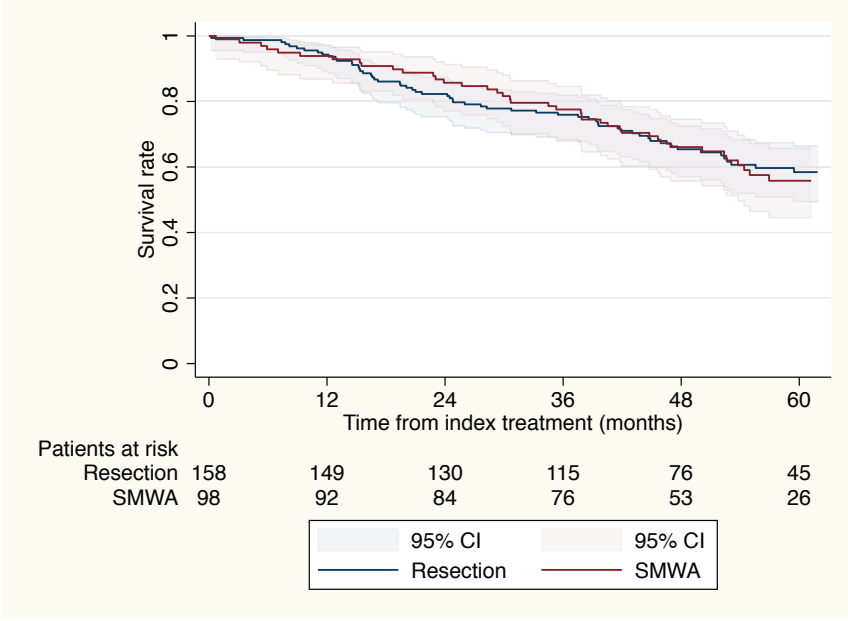

Figure 33. Relative overall survival curves of patients treated with SMWA (red) or resection (blue) for CRLM

Cox regression analysis confirmed no significant change in the hazard of death induced by the type of treatment (SMWA versus resection, HR 1.020 (CI 0.689 to 1.510), p = 0.921). Multivariable analyses yielded the primary CRC tumour stage (T stage), higher ASA classes and CCI categories and the tumour size to affect OS after treatment of CRLM (Figure 34).

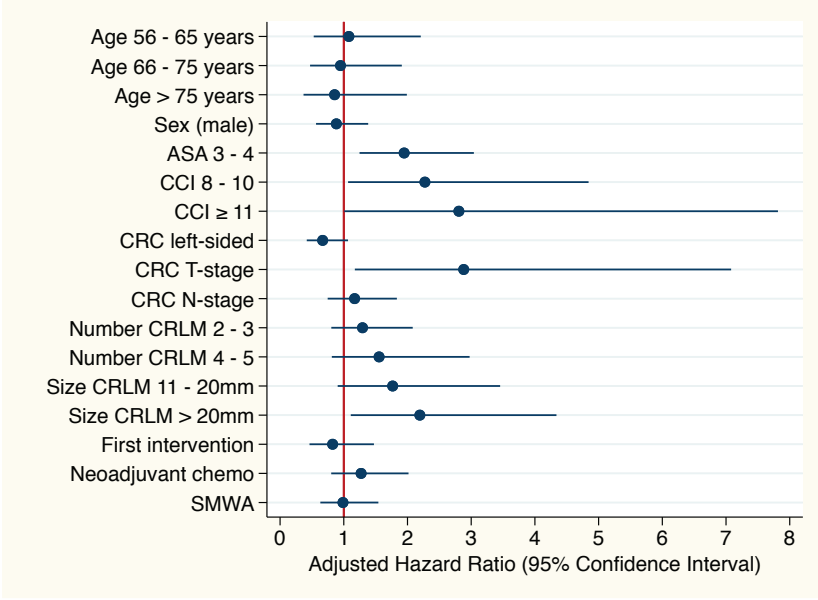

Figure 34. Coefficient plot showing the relative mean effect and 95% confidence intervals of baseline characteristics and treatment type on the hazard of death (Reference categories not shown)

Overall and major complications within 30 days were 30% versus 10% (percentage decrease 67%) and 10% versus 2% (percentage decrease 80%) in the resection versus SMWA cohort respectively (p < 0.01). The two major complications in the SMWA cohort included a haemothorax requiring drainage and a mortality from cardiac death 21 days after SMWA complicated by a liver abscess with gastrointestinal fistula. This patient underwent SMWA for two CRLM located in a subcapsular position in liver segments VII, and developed a liver abscess on day 17, treated with antibiotics and revised surgically for a related gastrointestinal fistula.

The 3-year OS in the matched patients (n = 158) and the patients that remained non-matched (n = 534) in the resection cohort was 76% (CI 69 to 82%) versus 70% (CI 66 to 73%) (p = 0.346), suggesting an adequate and representative sample selection as the matched control cohort.

6 Discussion

6.1 Thermal ablation as alternative to sugical resection

Studies I, III and IV focused on the analysis of oncological and economic outcomes after the treatment of small CRLM with TA, and specifically MWA or SMWA, in comparison to the gold standard surgical resection. Study I was a retrospective, PS-matched comparative analysis using population-based data extracted from a nationwide Swedish patient registry. Studies III and IV were prospective cohort studies, comparing data from a prospectively included and observed study cohort of patients treated with SMWA with contemporary control cohorts of patients treated with resection. To the best of our knowledge and up to the time of thesis writing (April 2023), Study I is the first PS-matched study using population-based data for the comparison of TA versus resection for CRLM. Study IV is the first prospective study reporting OS outcomes of patients with *resectable* CRLM deliberately treated with TA. Equally, Study III is the only available study comparing outcomes after TA versus resection in data arising from a *quasi-randomised* setting. In this methodological sense, the reported results from Studies I, III and IV represent *novel* findings in terms of enhanced internal validity on the subject of TA versus resection for CRLM to date (see also chapter 6.3).

Efforts of clinicians and researchers around the globe trying to create evidence supporting the use of TA as a valid alternative to resection for patients with CRLM are increasing (Figure 18). Two to three decades ago, research around TA for CRLM was focused on patients not qualifying for surgical resection, where significantly better outcomes were shown for patients treated with TA as opposed to chemotherapy alone[73]. Improved outcomes from larger series using more modern ablation technology including MWA further encouraged the use of TA for a broader patient population, including patients with potentially resectable CRLM, and corresponding research efforts. As the target population of CRLM patients qualifying for curative-intent treatment is increasing and becoming older with more severe comorbidity, low-morbidity treatments potentially reducing the time spent in healthcare facilities are gaining further importance[344,470].

One of the two main clinical motivations to pursue research in favour of TA for CRLM are the striking advantages of TA in terms of reduced treatment related morbidity, which was confirmed in most recent comparative studies adjusting for inclusion bias, especially in terms of liver-specific and major complications (see also chapter 2.2). The findings from Studies I, III and IV confirm these results, with a statistically significant decrease in treatment related morbidity in both overall and major complications after TA, even in well-matched study and control cohorts with regard to patient comorbidities and performance indexes. The range of 2% to 7% major complications corresponded to the rates of 1.3% to 16% published previously[263,336,337,344–346]. Importantly, only one liver-specific complication occurred in the MAVERRIC study cohort, however resulting in a mortality with a major cardiac event after surgical treatment of a gastrointestinal fistula related to a post-SMWA liver abscess. The development of a liver abscess after MWA is a rare complication with an incidence described around 1% in a recent series, with significant

association with a history of sphincter Oddi manipulation, the presence of cholangiocarcinoma, prior trans-arterial radioembolization and abnormal serum alkaline phosphatase levels[471]. None of these risk factors were present in the MAVERRIC study patient, who ultimately died from a major cardiac event following the septic complication.

The other main motivation is the parenchyma-sparing treatment characteristic of TA, favouring re-treatments in case of intrahepatic CRLM recurrence. In Studies I and IV using data from the SweLiv patient registry, no information was available on the incidence or type of liver recurrence. However, hepatic re-treatments were significantly more frequent after MWA and SMWA as opposed to resected patients in both studies. It may be assumed that these were performed for hepatic recurrences in the majority of cases. Study I showed that most re-treatments were re-TA in the MWA group, while most first re-treatments were re-resections in the resection group, with TA following as a second re-intervention. In Study III, liver-specific and overall recurrence rates were available in both cohorts, and RFS was significantly shorter after MWA versus resection, while DFS was similar in both groups. Contradicting results are reported in this regard (see Table 3), with more recent comparative studies showing no difference in RFS / DFS after TA or resection, and some favouring resection. It remains unclear if the mere incidence of liver-specific or other recurrences after curative-intent treatment of CRLM ultimately affects OS. In study I, only 14% of patients treated with MWA as a first intervention had resection as a consecutive treatment, suggesting that OS was not greatly influenced by subsequent resections in this group. In the literature, several studies showed no effect of RFS and DFS on OS after resection or TA for CRLM, however, *immortal time bias* must be considered in studies reporting OS after repeat interventions, potentially limiting the validity of results if not accounted for[373]. Equally, the effect of radicality of the initial CRLM treatment on RFS and OS has been questioned, further supporting the hypothesis that neither the type of initial treatment nor RFS significantly affect OS[472]. It seems that the type of recurrence pattern and the possibility for re-treatments with curative intent weight more heavily than the incidence itself[178], and RFS was therefore reported as an inadequate surrogate endpoint for OS in clinical research around CRLM treatment[70].

The overall incidence of recurrences in patients treated for CRLM is well-reported and described around 70%, of which around 50% will be re-treated, regardless of the type of the initial treatment (resection or TA)[70,120,132,169]. TA is accepted as a valid option for repeat treatments in case of hepatic recurrence, with similar OS but favourable morbidity rates and LOS as opposed to resection[173–175]. To opt for the lowest-morbidity, parenchyma-sparing treatment modality also as the *initial* treatment seems rational, especially when considering the short median RFS period of 1.3 years[70], and the increased hepatic tolerance to interval chemotherapy when reducing the loss of healthy liver parenchyma[473]. These aspects are crucial in an era of multimodal and repeat treatment strategies for patients with good prognosis CRLM disease and OMD, resembling more of a chronic disease than end-stage cancer[473]. The positive effect of reduced morbidity on OS and DFS[121] might also interact with a potential negative effect of RFS and DFS on OS, but the analysis of causalities and interactions in this complex clinical setting is difficult.

The quest to prove the value of TA as a valid alternative for initial CRLM treatment thus lies in showing non-inferiority in terms of OS compared to surgical resection. This was chosen as the primary endpoint for the MAVERRIC trial and the main outcome for Studies I and III. One of the crucial issues limiting the validity of most retrospective studies comparing TA to surgical resection, is the severe methodological constraint of inclusion bias (i.e. confounding by indication). In other words, the very factors known to affect OS after treatment of CRLM, such as higher age or more severe comorbidity, are also the reasons for choosing the treatment in the first place. This undoubtedly influenced the significantly shorter OS found after TA in most earlier non-matched retrospective series, and is highlighted as the main reason for a limited comparability in all recent meta-analyses, together with between-study heterogeneity in treatments and outcomes[148,350,420] (see also chapter 2.2). This was confirmed in Study I, where baseline characteristics describing "older, more comorbid patients with more extensive disease" were significantly more common in patients treated by MWA as compared to surgical resection in the baseline population. PS matching yielded two comparable groups in terms of baseline characteristics, certainly reducing selection bias markedly. The resulting similarity in 3-year OS rates align with results from the other six available studies applying PS matching for the comparison of OS after TA versus resection[338,360,394–397] (see Table 3). While some of the other PS matched studies had similar inclusion criteria in terms of CRLM number ≤5 and size ≤ 3cm[338], others used slightly different criteria (CRLM number ≤ 3 and size ≤ 5 cm or CRLM number 5 and size ≤ 5 cm[395–397]), or no restriction[360,394], but all adjusted for number and size criteria in the PS creation or as confounder in multivariable analyses.

The resulting 3-year OS rates in the resection cohorts between 70% and 76% in Studies I, III and IV were located at the higher end of the range reported in the literature, described between 30% to 80%, with a median of around 58% (and around 66% for solitary CRLM), in a meta-analysis of 64 studies[68]. They corresponded however to 3-year OS rates after resection of around 70% reported in studies with the same inclusion criteria regarding the extent of CRLM disease (≤ 5 CRLM of ≤ 3 cm)[338]. Similarly, the 3-year OS rates after MWA in Studies I, III and IV between 75% and 78% were situated at the higher end and even above rates from previous studies, summarised to range from 60% to 70% in two recent meta-analyses[334,343]. In another study reporting outcomes after TA for technically *resectable* CRLM using MWA additionally to RFA, 3-year OS was 60%, however including CRLM up to 5cm[398]. Reasons might include the use of stereotactic navigation technology, which is known to enhance technique efficacy[309] and allows a highly standardised treatment technique, in Studies III and IV. Also, the treatment of patients with CRLM is highly centralised in Sweden and performed in only a few specialised HPB centres throughout the country, potentially enhancing outcomes after both TA and resection for patients with CRLM (Study I)[474]. Overall, the between-study comparison of univariable survival probabilities from Kaplan-Meier curves is limited due to heterogeneity in patient populations, in the extent of CRLM disease and related treatments, in procedural factors and in local treatment guidelines. The comparison of effect sizes and results from multivariable analyses remains therefore crucial. The finding that the type of treatment did not affect OS while adjusting for confounders underlined findings from Kaplan-Meier

curves in Studies I, III and IV. Factors found to influence OS after TA or resection corresponded to factors previously described in the literature (see also chapter 1.2.4 and Table 2), including clinical (age, comorbidity indexes, Studies I and IV), primary CRC tumour T and N stages (Studies I and IV) and CRLM number and size (Studies I, III and IV). Despite varying definitions and categorisations with different cut-offs applied also throughout the literature, the size of treated CRLM remains one of the most frequently described characteristics affecting OS in CRLM treatment, even within the already restrictive definition of a size ≤ 3 cm, as shown in Studies I, III and IV.

The advantages of reduced treatment related morbidity and especially also LOS (Table 3), suggests that TA may be beneficial to healthcare systems also in terms of treatment related costs and health related QOL. Significantly shortened LOS durations after TA versus resection for CRLM were confirmed in Studies I, III and IV. On the other hand, reports on health economic efficacy and QOL after resection or TA for CRLM, and comparisons thereof, remain scarce. Regarding QOL, Ruers et al.[349] assessed QOL in CRLM patients using standardised questionnaires, showing a significant decrease in health related QOL 3 weeks after open combined resection and ablation (RFA or cryoablation) versus palliative chemotherapy, which was fully restored within 3 months of ablation and resection, but remained lower throughout 12 months in the chemotherapy group. Using the QOL data from Ruers et al., another group showed enhanced quality-adjusted life expectancy in CRLM patients > 70 years with comorbidities, when treated with RFA as opposed to resection[475]. A detailed health related QOL assessment in Finnish CRLM patients throughout different treatment phases was presented by Lehtomäki et al.[476], showing similar QOL scores to the general population after curative-intent CRLM treatment. In all three studies, local ablation was a heterogenous group of various local ablative treatments combined with resection. Regarding cost effectiveness, a model-based comparative analysis suggested that MWA might be associated with reduced costs but also inferior outcome compared to resection, while RFA for solitary CRLM < 3 cm was potentially superior in terms of costs effectiveness per quality-adjusted life years (QALY) gained[470]. However, data on MWA were derived exclusively from the methodologically questionable RCT by Shibata et al.[393], and data on QOL and costs from a prior study by Gazelle et al[400]. The latter study reported superiority of resection over RFA in terms of QALY's gained, however none of the underlying QOL data was extracted from patients with CRLM or using validated questionnaires. The same data was used by Froehlich et al.[399], suggesting MWA as the most cost-effective strategy as opposed to resection and RFA in intermediate to high resource settings.

In the MAVERRIC trial, data on QOL was not assessed and together with the lack of high-quality data on QOL after TA of CRLM available from the literature, it was decided against conducting formal health economic analyses on cost effectiveness and QALY's gained. However, the analysis of healthcare related costs in the quasi-randomised setting in Study III allowed to compare the true costs related to the index treatment and within 2 years of prospective follow-up, in a patient population with similar baseline characteristics including healthcare consumption one year prior. The enhanced overall costs in the resection cohort were related mainly to the index treatment inpatient hospital

admission, and prevailed despite SMWA patients requiring a more expensive radiological follow-up and more (mainly ambulatory) re-treatments within 2 years. Importantly, this included the use of the most modern technological standards using stereotactic navigation for MWA of CRLM, which is often highlighted as a critical aspect with regards to enhanced procedural costs. While the crucial economic effort when using such technology is related mainly to the initial acquisition of the navigation device and corresponding software, the use of disposable ablation antennas was included in the total costs for inpatient hospital admissions in Study III. Other reports even highlight the use of navigation technology for TA with regards to cost effectiveness[477]. In parallel with the shorter LOS, admissions to rehabilitation facilities after index treatment were not required after SMWA, further reducing the overall time spent in medical facilities. This, the overall reduced healthcare related costs and similar OS compared to resection highlighted significant advantages related to SMWA treatment for CRLM patients.

6.2 Computer-based innovation in hepatic thermal ablation

The field of *radiomics*, or novel solutions in health informatics and artificial intelligence (AI), are expected to transform the practice of radiology including IR in the near future[478]. The area of image-guided IR interventions for liver tumours presents an optimal environment for the development of novel technological solutions to enhance the therapeutic performance (efficacy and safety) via improvement of accuracy, efficiency and standardisation of these procedures (see also chapter 1.4, Figure 10). This is due to the established use of computer-based imaging such as CT as the image-guidance modality, in an environment of minimal tissue deformation during the procedures. The advantages of using stereotactic navigation technology to enhance accuracy for tumour targeting was initially advocated by just a few groups in specialised centres, mainly also developing novel navigation technology together with engineering facilities. Over the last decades, the advantages of stereotactic TA were recognised by a broader generation of physicians from different specialities, interested in innovative solutions in IR. With increasing experience in the use of stereotactic navigation technology for TA, advantages compared to traditional *free-hand* image-guidance became quantifiable, confirming enhanced targeting accuracy and treatment efficacy[309] (see also chapter 1.4.1).

When designing the multi-centre prospective MAVERRIC trial, the use of stereotactic navigation technology for MWA was deliberately chosen as the comparator to surgical resection, applying the highest available standards for TA therapy. The positive experience with SMWA from the three participating centres certainly played a role in doing so, encouraging the aim to investigate its potential as a potentially curative treatment option for patients with CRLM[252,289,307]. One of the driving credos was that the use of stereotactic navigation allows to enhance inclusion criteria for MWA treatment, which is often limited by traditionally "difficult-to-target" intrahepatic tumour locations. While no comparative studies explicitly investigate the eligibility of malignant liver tumours to TA as the outcome of interest, prior series have shown that stereotactic TA

allows safe and effective treatment of hepatic tumours e.g. in the caudate lobe or in subdiaphragmatic positions[252,284]. Accordingly, patients with tumours located in all liver segments were eligible for inclusion into the MAVERRIC trial, including 3 tumours in the caudate lobe, 49% in subcapsular locations and the majority (56%) in subdiaphragmatic liver segments VII and VIII. In that sense, using SMWA certainly allowed eligibility to a potentially curative treatment not restricted by tumour accessibility for safe targeting. A recent consensus-based guideline defined "ablatability" criteria for curative-intent treatment of CRLM, suggesting that a central tumour location is a valid criterion to prefer TA as opposed to resection for small, potentially resectable tumours[326,386]. Following the concept of a parenchyma-sparing, avoiding major hepatectomies for patients with few but deep-seated CRLM, this was agreed upon with low-level evidence but with strong-level expert consensus[326]. Specifically for central lesion locations, choosing the most accurate targeting trajectories is crucial to avoid harm to central vascular and biliary structures[241], supporting all efforts to enhance accuracy using precision technology tools. These will allow to counteract the previously reported higher LR rates when using a percutaneous "free-hand" versus a surgical approach (see Table 2). Other aspects enhancing eligibility to TA treatment when using stereotactic technology, are the possibility to target DLM[287,449], and the efficient positioning of multiple ablation antennas for treating larger tumours and facilitating other local ablative methods such as IRE[479].

The above-mentioned consensus paper highlighted the crucial need for standardisation in TA of CRLM, including the definition of criteria for treatment eligibility, feasibility and optimal efficacy, especially in light of the current heterogeneity in treatment strategies for TA[326]. This is a crucial factor hampering the design of meaningful trials in surgical oncology and thus generalisability of results[480]. The aim of standardisation is to enhance treatment reproducibility, allowing comparability of results, improving inter-societal communication and promoting collaborative research efforts for guideline development, towards optimised treatment decisions and predictable patient outcomes. Introducing navigation technology and innovative computer-based solutions for TA, takes the possibilities of standardisation to the next level also from a procedural aspect. The simplicity and straightforwardness of procedural workflows and the related consistency in achieved results allows for reproducible outcomes, reducing inter-operator variance, which is a known factor influencing outcomes after TA[481]. After initial training in procedural workflows and in hardware set-up, relatively steep learning curves can be achieved when introducing the use of navigation technology[275,287]. This contradicts previous concerns of increased complexity when using such novel technology[262]. A remaining drawback is the current lack in accuracy and specificity of outcome definitions for TA[335], hampering the comparability of results and needing urgent re-consideration with international consensus. Once digitalised tools for objectified and reproducible outcome assessment will become available on a broader scale, this will hopefully encourage a revision towards more standardised outcome definitions. This is crucial especially in an era of exploding technological development with immense variety in available novel solutions and high pace with which those are introduced (see also chapter 8).

More sophisticated solutions based on radiomics become available for evaluation of treatment success, i.e. the control of complete tumour ablation, including analyses on tumour necrosis and ablation margins[482–485]. We previously developed a novel tool for volumetric QAM computation[323], which can be integrated into SMWA procedures alike the ones applied for patients included into the MAVERRIC trial. In Study II, we applied the 3D QAM tool retrospectively, while at the time of intervention, margins were assessed visually by overlay of pre- and post-ablation scans. The quantification and objectification of obtained ablation margins with 3D-QAM yielded relatively low margins, highlighting a potential overestimation of margins evaluated by visual overlay. When adjusting for other factors known to predict LR, ablation margins remained the main and most relevant factor affecting LR. This aligned with previous studies describing ablation margins as the main predictor of LR after TA of CRLM, next to tumour size (see Table 2). While earlier studies using 2D assessment of ablation margins suggested 5 to 10 mm as the minimal margin to avoid LR, results from Study II suggest a smaller and more precisely defined margin, aligning with other groups reporting quantitative margins[486]. Importantly, the proposed 3D-QAM algorithm allowed to adapt for a systematic under-estimation of quantitative volumetric ablation margins for tumours located in subcapsular positions. Other factors related to tumour biology described to affect LR in previous studies, such as KRAS mutational status or perioperative chemotherapy, were not significant in our model, potentially due to a shorter observation period.

While a semi-automatic tool was applied for segmentation of tumour and ablation volumes in Study II, it is likely that more comprehensive algorithms incorporating AI will provide tools for automatised segmentation, computation and evaluation of results during IR treatments[487,488]. Meanwhile, an integration of 3D-QAM into SMWA workflows will enable immediate evaluation of treatment success and re-ablation if necessary, towards a 100% technical success rate and avoiding time delays in outcome assessment, similar to frozen sections during surgery. Volumetric QAM determination will also allow to differentiate between incomplete ablations and *true* LR at the ablation site, while currently, most reported LR rates probably contain a degree of misdiagnosed incomplete ablations. Incomplete ablations can be diagnosed at the exact tumour location in 3D using 3D QAM[484] and need immediate re-ablation, while true LR arising from satellite lesions in the vicinity of CRLM, alike other micro-metastases in the liver, are best addressed by systemic therapy. With the current definition of LR, the 17% LR rate in Study IV corresponded to previously reported rates around 18%[334] but was rather high and probably influenced by a 70% rate of concomitant new intrahepatic CRLM, indicating aggressive CRC biology.

Overall, increasing expertise with novel technological solutions will continue to enhance eligibility of patients to TA treatments, improving consistency of treatment success and allowing customisation of TA therapy in an era of personalised medicine. The latter includes the design of personalised ablation volumes bespoke to individual tumour shapes, using novel algorithms allowing an automated adaption of ablation energy delivery and ablation probe velocity[489]. Based on the herein presented results, it can be expected that technological innovations such as stereotactic navigation and radiomics

will become an integral part of the multimodal management for patients with CRLM, expanding the limits of curative intent treatments for these patients.

6.3 Methodological considerations and limitations

In clinical and epidemiological studies, the value of findings can be assessed by analysing the *validity* and the *precision* of the obtained research results separately[490]. Four types of validity are discussed according to Figure 35.

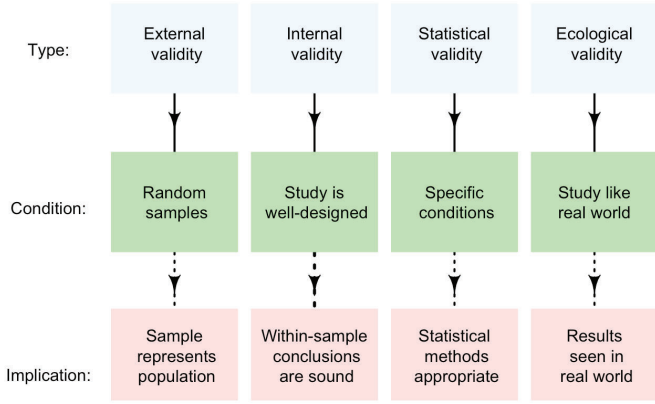

Figure 35. Four types of validities in clinical studies. Reprinted with permission from[491] (non-adapted material, Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Public License, https://creativecommons.org/licenses/by-nc-sa/4.0/legalcode)

The *external validity* or *generalisability* of a study is the extent to which the study results are applicable to the entire population from which the sample is drawn (in our case, patients with (potentially resectable) CRLM). It depends on the internal validity and on factors such as eligibility criteria, response rate, the study setting, and the exposures and outcomes studied. It reflects the *accuracy* or *trueness* of the sampling method, i.e. how close the sample estimate lies to the population average, and is affected by how random the sample is chosen from the entire population. In an epidemiological sense, none of the samples in the current studies were chosen randomly, since the participating centres and their geographical locations were restricted, however, truly random samples on a global scale are almost impossible to obtain in medical research. Study I was a population-based analysis of data from a Swedish nationwide registry, with high (97%) representation of the overall Swedish population of patients treated for CRLM. This suggests that the sample is more representative for the intended population (i.e. has lower *sampling bias*), when compared to samples drawn e.g. from individual centres. In Study IV, the external validity and accuracy of the sample (MAVERRIC study group) is lower, since data were obtained from a selected group of patients included into the MAVERRIC study, however, it included consecutive patients from three European tertiary HPB centres (or a centre linked to a local MDT from a tertiary centre). In Study II, selection of a subgroup of included lesions

qualifying for the analysis lowered external validity of the findings. Equally, data from one centre was analysed in Study III, potentially lowering external validity.

The *internal validity* or *effectiveness* of a study is the extent to which the study by its methodology measures what it was supposed to measure, following the definition of its hypotheses and aims. In other words, it addresses the question whether the study allows to isolate the relationship of the exposure on the outcome, by eliminating all other possible explanations. If given, this allows a meaningful inference to an underlying truth or *theta* (i.e., a true distribution of possible outcomes on a population level). Different kind of *bias'* may cause systematic differences between the obtained sample statistics and theta, leading to misinterpretation of observed findings and false conclusions. The study design greatly influences the chance of bias and the possible ways to adapt for it, such as the bias related to data collection called *selection bias,* or extraneous factors affecting both exposure and outcome called *confounders*. Study IV addressed selection bias in its design by deliberately assigning SMWA to patients amenable to both treatment types, and by doing so addressed *confounding by indication*, i.e. confounders both influencing the choice of treatment and the outcome (i.e. age, comorbidities) by *restriction*. A potential variation in the understanding of resectability and ablatability between physicians and thus in study inclusion of patients at the MDT conferences might have persisted. Also, data on CRLM ablatability in patients who underwent resection from the control group, was not available from the Swedish registries. Without doubt, a *random allocation* of the exposure (TA versus resection) would be the strongest design to study its effect on the defined outcome (3-year OS), as this would also account for unknown and unmeasured confounders. It was decided against an RCT at the time of the MAVERRIC study design, based on the difficulties linked to study design and execution (see also chapter 8). In Study III, the alternating treatment allocation every other week led to a *quasi-randomised* setting, applying the same selection criteria to both groups (patients with ≤ 5 CRLM ≤ 3 cm amenable to both resection and SMWA). Despite the retrospective decision to analyse data within this Swedish subgroup of the MAVERRIC study, this study design enhanced internal validity of results.

Confounding was further addressed by choosing *statistical analyses* allowing to adapt for bias to a certain degree and enhance internal validity. Minimising confounding in observational studies would require that all or most variables suspected as being confounders can be measured. In parallel with the above-mentioned advantages on external validity, using population-based registry data can limit internal validity by restricting the availability of data to those previously collected, thus potentially hampering the possibility to adapt for confounders in statistical analyses. In Studies I and IV, some confounders known to potentially affect both treatment choice and OS in patients with CRLM (see also Table 2) were not available from the Swedish registries, including pre-treatment carcinoembryonic antigen (CEA) levels, biomarkers such as KRAS mutational status, and details on chemotherapy regimen and extrahepatic disease spread. These factors could not be accounted for in the design of the propensity scores or in multivariable regression analyses, lowering the internal validity of findings. Some factors such as KRAS mutations could on the other hand be included in the statistical

model in Study III, which did not significantly alter the effect of the treatment type (TA versus resection) on the outcome. The PS models were designed to maximise bias reduction (see chapter 4.2) while keeping in mind study precision (see below). Different model specifications yielded similar results in the effect size of the treatment type on OS, strengthening the argument of adequate internal validity. Also, a potential introduction of new bias by the PS matching itself was investigated and interpreted as non-significant.

Other data not available from the Swedish registries, which would have added value to the understanding of factors affecting OS after the studied index treatment, were data on tumour recurrence and reasons for hepatic re-treatments. Data on the number and type of re-treatments (MWA and / or resection) after the index treatment were however available, and potentially affected the outcome of OS to a degree that we could not measure in the current analyses. Also, the index treatment was not the first hepatic treatment for CRLM in all patients in Study IV, which was only partially accounted for by adding this factor in the PS model design / multivariable analysis, potentially affecting internal validity of results. Overall, the fact that Studies I, III and IV found similar effect sizes of resection versus SMWA on OS, while applying varying study designs and populations (although overlapping), strenghtens both internal and external validity of results. The statistical analyses applied in Study II were aimed to enhance internal validity by using population-average GEE models and robust estimators of variance (see also chapter 4.2).

The *statistical validity,* describing the adequacy to apply certain statistical methods to a certain sample and scientific question, and the meaningfulness of obtained results and CI's for inference to the population parameter and theta, was investigated by testing various assumptions underlying the applied statistical models (see also chapter 4.2).

The *ecological validity* or *practicality* of a study describes how well the study design and context approximate the "real world". This is generally enhanced in observational, and especially population-based analyses, as opposed to an RCT designs, where inclusion and exclusion criteria are strict and may not apply in the real world[480]. Using SMWA as opposed to the currently more broadly used traditional image-guidance for TA of CRLM, might hamper practicality on a global scale, and must be taken into account when discussing results in the general context of TA versus resection for CRLM. This represents a general challenge when introducing novel technology in medicine (see also chapter 8). Equally, even though the QAM algorithm was designed to be applicable for any type of image-guided TA, it would be more difficult to integrate it into workflows who do not use stereotactic navigation technology, in which case deformable registration software would be required[492]. Further studies using similar and different stereotactic navigation and treatment evaluation technology will need to confirm the current findings and address potential *novelty bias*[493]. Another limitation potentially affecting internal validity of Study II through *measurement bias* is the known tissue shrinkage occurring immediately after MWA[494], prior to expansion of ablation volumes thereafter, which might have led to an underestimation of QAM computed on the immediate post-treatment CT scan.

The *precision* describes the variation in sampling estimates from different samples, i.e. the extent to which errors occurring by chance (random errors) affect the results of a study. Precision depends mainly on i) the *sample size*, with more observations leading to more precise sample estimates, represented by narrower CI's, and ii) the *efficiency*, considering aspects such as a balanced distribution of patients across "exposure" groups, or the number of outcome events per independent variable and their degree of freedom (events per variable (EPV))[495,496]. In Studies I, II and III, the sample sizes were not based on calculations aiming for a certain statistical power, but restricted to data available from the registries, selected over a recent time period to avoid *chronological bias*[493]. As a result, the sample sizes of patients in both treatment groups were fairly small in Studies I and III, with resulting wide CI's around the point estimates of 3- and 2-year OS, respectively. This equally applied for analyses of RFS and DFS in Study III. In parallel, EPV's in Cox analyses were 3 and 4, respectively, and thus below the rule-of-thumb of 10 to 20[496] to avoid overfitting of the model. These factors lowered the precision of findings in both studies. In Study II, the number of CRLM qualifying for analysis of QAM in the GEE model (n = 65) and outcome events (n = 10 patients with ASR) were small, yielding very large CI's and also limiting precision of estimates. Future clinical research investigating QAM in prospective studies of larger sample size will be necessary to verify its effect on LR after TA. In Study IV, the calculated sample size of n = 92 (Figure 22, chapter 4.2) was met, with a total of 98 patients qualifying for analysis and conveyed to the final sample after PS matching. It can therefore be assumed that the power to show non-inferiority in this study was given, and that the corresponding CI ranging from 68% to 85% around the point estimate of 78% 3-year OS probability in the SMWA group was adequately precise (Figure 33). The EPV of 6 in the Cox regression model was below the rule-of-thumb of 10 to 20[496], but within a relaxed definition of 5 to 9 described as adequate in many scenarios[497].

In summary, *external validity* and *ecological validity* were high especially in Study I, using nationwide population-based data, *internal validity* and bias control were adequate especially in Study III and IV based on study design, *statistical validity* was sound within the known limitations of statistical inference, and *precision* can be considered adequate in Study IV, with potentially limited power in Studies I, II and III.

7 Conclusions

Findings from Studies I, III and IV suggest that OS of patients with small CRLM is not inferior when treated with MWA as opposed to surgical resection. Study IV specifically showed similar 3-year OS after SMWA in patients with liver metastases amenable to both MWA *and* surgical resection. Study III confirmed similar OS despite a shorter RFS leading to more frequent hepatic re-treatments. The known advantages of significantly lower treatment related morbidity and shorter LOS related to MWA versus resection were confirmed, and together with less frequent admissions to medical facilities, allowed a reduction of overall healthcare related costs within two years of treatment (Study III). This supports a probable shift towards using low-morbidity, parenchyma-sparing treatments associated with decreased time spent in medical facilities as initial treatments for patients with CRLM. This will also gain importance with rapid advancements in diagnostic and therapeutic technologies leading to earlier tumour detection and longer courses of disease, in an overall ageing population with higher comorbidities but potentially qualifying for treatments with curative intent. In this context, current findings might aid decision-making when designing treatment policies and defining personalised algorithms for patients with CRLM.

Innovative technologies such as the applied stereotactic navigation technology (Studies II, III, IV) and the investigated QAM algorithm for evaluation of treatment success (Study II) address the increasing demand of enhanced therapeutic precision and reproducibility in outcomes when using MI cancer treatments. Findings from Study II underlined the utility of a novel algorithm for QAM assessment and its potential to enhance local tumour control in TA. This can serve as an additional tool for the development of refined definitions for standardised reporting of outcomes after TA of CRLM.

8 Points of perspective

The global burden of CRC and CRLM has been increasing worldwide and will likely continue to do so over the next decades. Advancements in diagnostic and therapeutic approaches in an ageing population is leading to a higher prevalence of earlier disease stages also within stage IV CRC. The high response rates to treatments with curative intent and high survival probabilities reported in patients with OMD despite high recurrence rates, led to the notion of considering CRLM disease as a chronic disease rather than end-stage cancer. Despite the general trend for de-escalation towards MI, low-morbidity and parenchyma-sparing treatments[473], the acceptance of TA and its integration into clinical guidelines has been slow. The role of TA for CRLM treatment is still not adequately debated in international conferences, despite growing evidence of excellent oncological and advantageous clinical results. The lack of available RCT's is a key argument, yet when put into perspective on the proportion of surgical oncology treatments which are based on RCT's, (the proportion of phase III trials in surgical publications is around 8%[480]), this is most probably not the only factor hampering the acceptance of TA. Several RCT's have been designed, some abandoned and some not yet completed (see also chapter 2.1).

The challenges adhering to the conduct of phase III trials in surgical oncology, and even more so in surgical innovation, are well known, including the difficulty of procedure standardisation, of achieving good quality controls, of patient accrual (one in five RCT in surgical oncology is discontinued due to poor recruitment[498]), of administrative and financial efforts and importantly, of reaching *clinical equipoise* towards both treatment types[480,499]. The latter affects the controversy around TA versus resection in particular, since it is requires for curative-intent treatments performed by clinicians from different specialities (i.e. resection by surgeons versus TA by interventional radiologists)[430]. Together with heuristic reasons of dispositional decision-making[500] and a transfer in logistic resources, this might be the crucial factor hampering patient recruitment for RCT's, and equally, a perception of TA as a valid treatment alternative. Surprisingly, the recognition of TA and integration into joint clinical guidelines was much faster in the even more multi-disciplinary field of primary liver cancer. A reason might be the traditionally more established role of decision-making by hepatologists as opposed to surgeons in HCC treatment. Results from the soon-to-be-completed COLLISION trial[174] will ultimately show if RCT data will achieve an acknowledged perception and application of TA as an alternative to surgical resection on a broader scale.

In parallel, innovation in medical technology grows exponentially with increasing pace, enhancing the above-mentioned challenge of designing valid studies and creating high-level clinical evidence. Designing phase 3 trials to prove advantages of novel technology over standard approaches is immensely challenging, and currently impedes the adoption of novel techniques into clinical practice[480,499]. Despite a core design unsuitable for non-pharmacological research, and relevant limitations such as a lack of generalisability, phase III studies are still seen as the only possibility to create level I evidence also for surgical treatments[480]. International research groups addressed these challenges by designing a methodological framework for the creation of evidence around surgical innovations

(IDEAL)[501]. Addressing the trade-off between high-level evidence and study feasibility, progressive researchers highlight the importance of pragmatic alternatives, hoping that surgical oncologists will recognise the necessity to end the monopoly of RCT research and broaden acceptance to alternative prospective methodologies[480]. These include e.g. international collaborative efforts and well-designed, open-access patient registries capturing technical details and pitfalls, and prospective development studies (e.g. SURCARE[502]). Despite these hurdles, it can be expected that TA enhanced by computer-assisted and robotic technology will likely become an integral part of the constantly enlarging toolbox of available molecular, immunological and interventional treatments for CRLM. A comprehensive understanding of each novel technology's safety and efficacy profile is crucial, and guidelines will need to include information on indication and application profiles. Next to technology aiming to enhance individual aspects of therapeutic functions (such as stereotactic navigation or treatment validation in TA), more comprehensive algorithms incorporating AI and machine learning will allow automatisation of workflows. As for all AI-based technology, the main challenge will be the incorporation of controlled interfaces and checkpoints for feedback and human intervention. Aiming towards a comprehensive robotic system for TA, we are currently developing an algorithm creating dynamic ablation volumes bespoke to individual tumour shapes, to be integrated in a fully automated treatment model for personalised TA[489].

Modern AI-based algorithms further revolutionise the potential to develop decision-trees for personlised treatment algorithms not limited by the complexity of disease presentation, severity and chronology and the multitude of factors predicting treatment success. The latter will increasingly also include a variety of molecular and immunological markers and innovative *imaging biomarkers*[136,503–507]. It will further allow the integration of more complex outcome measures, potentially more adequately representing what affects patients as a whole and as part of a health societal structure, than the currently mostly applied outcome measures of RFS, DFS and OS. This will include patient-reported outcomes such as aspects on QOL and patient resilience, and on health economic relevance and cost effectiveness. Integrating AI algorithms into decision-making processes will allow an adequate integration of the immense complexity of influencing factors and targeted endpoints in cancer research. For patients with CRLM, this might eventually also allow a more refined understanding of treatment with *curative intent*, beyond a classification of *resectable* versus *non-resectable* at presentation and during the later course of disease - toward more individualized and patient-focused therapeutic pathways.

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10 References

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