From the Department of Clinical Sciences, Danderyd Hospital,
Karolinska Institutet, Stockholm, Sweden

LIVER METASTASES FROM COLORECTAL CANCER

Jennie Engstrand

Karolinska Institutet

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Cover: Reconstruction of pre-operative computed tomography scan on a patient with previously ablated tumours and present tumours to be ablated.
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Liver Metastases from Colorectal Cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Jennie Engstrand

Principal Supervisor:
MD, Associate Professor Jacob Freedman
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital (KIDS)
Division of Surgery and Urology

Co-supervisor(s):
MD, Associate Professor Eduard Jonas
University of Cape Town Health Sciences Faculty
Department of Surgery, Groote Schuur Hospital
Division of Surgical Gastroenterology

MD, PhD Henrik Nilsson
Karolinska Institutet
Department of Clinical Sciences,
Danderyd Hospital (KIDS)
Division of Surgery and Urology

Opponent:
MD, Professor Rowan W. Parks
University of Edinburgh, United Kingdom
Department of Surgical and Clinical Sciences,
Royal Infirmary of Edinburgh

Examination Board:
MD, Associate Professor Christian Sturesson
Lund University, Skåne University Hospital
Department of Clinical Sciences Lund
Division of Surgery

MD, Associate Professor Jan-Erik Frödin
Karolinska Institutet
Department of Oncology and Pathology,
Karolinska University Hospital
Division of Oncology

MD, Associate Professor Annika Sjövall
Karolinska Institutet
Department of Molecular Medicine and Surgery,
Karolinska University Hospital
Division of Colorectal Surgery

Till

Isabelle och Johan

Medicine is a science of uncertainty and an art of probability.

Sir William Osler

ABSTRACT

Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide. At diagnosis of CRC 20-25% of patients have metastatic disease. The liver is the most common metastatic site and liver metastases are detected in 25-30% of all patients. A quarter of these patients are amenable for liver resection that results in a five-year survival exceeding 50%. The indications for liver resection continue to broaden and are no longer limited by number and size of liver metastases nor the presence of extrahepatic metastases. Currently liver resection is indicated when macroscopic tumour clearance can be achieved with preservation of a sufficient future liver remnant. Different strategies to improve resectability exist such as portal vein occlusion, two-stage resections, associating liver partition and portal vein ligation for staged hepatectomy and thermal ablation, mainly radiofrequency ablation or microwave ablation (MWA). Decisions on management of patients with metastatic CRC should ideally be made in a multidisciplinary team (MDT) setting. Failing to do so may result in suboptimal management and patients that could be resected are not necessarily offered curative-intended treatment. As a result of this there are known regional differences in the treatment of patients with liver metastases that may affect survival. For patients not suitable for resection, either due to the metastatic burden or comorbidity omitting extensive surgery, local ablation is an option.

Aims: The aim of *Study I* was to provide detailed population-based data of liver metastatic patterns, treatment and survival in patients with metastatic CRC. In *Study II*, the potentially improved resection rates were evaluated in a scenario where all patients with liver metastatic disease, irrespective of extrahepatic metastases, were assessed by a liver MDT. *Study III* aimed to describe the feasibility and safety of a multiple MWA strategy in patients with initially unresectable liver metastases. The primary aim of *Study IV* was to evaluate the accuracy and safety of antenna placement in stereotactic computed tomography-guided MWA of primary and secondary liver tumours. The secondary aims of *Study IV* were to evaluate the feasibility of the navigation system, to measure the procedure-related radiation dose and to assess the safety of high-frequency jet ventilation for target motion control.

Patients and Methods: In *Studies I and II*, a population-based cohort consisting of all patients diagnosed with CRC in the Stockholm and Gotland region during 2008, identified from the Swedish Colorectal Cancer Registry, was used. Details of metastatic spread, referral to a MDT conference and oncologic and surgical treatment were retrieved from electronic patient charts and recorded during a five-year follow-up period or until death. Predictors of survival in *Studies I and III* were estimated using a Cox proportional hazards model. Survival curves were illustrated using Kaplan-Meier estimates and survival functions were compared using the log-rank test (*Studies I-III*). For *Study II*, additional information on American Society of Anesthesiologists grade, comorbidity and patients' own preferences towards treatment, were retrieved for the 272 patients with liver metastases. Each patient was presented at a fictive liver MDT conference, irrespective of previous management, and categorized as resectable, potentially resectable or unresectable. Treatment decisions were

compared with the original management and factors associated with referral to the liver MDT were assessed using logistic regression. In *Study III*, a multiple MWA strategy was applied to 20 patients with initially unresectable liver metastases between October 2009 and September 2012. The feasibility and safety of the procedure as well as local recurrence rate was recorded. Overall and disease-free survival in the ablated group was compared with results from two historic cohorts from *Study I*, one treated palliatively and the other resected. In *Study IV* 20 patients with primary or secondary liver malignancy, where surgical resection was contraindicated or the lesions were not visible on ultrasound, were included for treatment with percutaneous MWA using a stereotactic navigation system (Cascination AG, Bern, Switzerland) that shows the actual position of the tracked antenna in real time with respect to pre-operative CT images. Descriptive statistics were used to evaluate the accuracy of antenna placement, the number of antenna readjustments, safety and radiation dose.

Results: In *Study I* 1026 patients with CRC were identified and liver metastases were detected in 272 (26.5%). Liver and lung metastases were more often diagnosed in hindgut (splenic flexure to rectum) compared with midgut cancer (caecum to splenic flexure) (28.4% versus 22.1%, p=0.029 and 19.7% versus 13.2%, p=0.010, respectively) but the extent of liver metastases was less for hindgut compared with midgut cancer (p=0.001). Five-year OS was significantly worse in liver metastatic midgut cancer compared with hindgut cancer (6.5% vs. 21.6%, p<0.001). In liver metastatic disease the presence of lung metastases did not significantly influence OS as assessed by multivariable analysis (HR 1.11, CI 0.80-1.53). At the fictive liver MDT in *Study II*, a further 22 patients (12.9%) of the 170 patients not previously referred to a liver MDT were considered as resectable or potentially resectable. Factors influencing referral to a liver MDT were age (OR 3.12, CI 1.72-5.65), ASA score (ASA 2 versus ASA 3, OR 0.34, CI 0.18-0.63) and number of liver metastases (OR 0.10, CI 0.04-0.22, 1-5 versus >10 liver metastases), while male gender (OR 1.39, CI 0.84-2.30) and treatment at a teaching hospital (OR 1.06, CI 0.62-1.81) were not. In *Study III*, the ablated group showed a four-year overall survival of 41% compared with 70% for the historic cohort of resected patients and 4% for palliatively treated patients. Eighteen patients had recurrence in the liver, 11 had extrahepatic recurrence and 10 out of 20 treated patients were alive at a median follow-up of 25 months. In *Study IV*, the antenna was placed with a mean target error of 5.8±3.2 mm in relation to the intended target at a mean total radiation dose of 958±557 mGy x cm.

Conclusions: *Study I*: Detailed population-based data on the metastatic pattern of CRC and survival could assist in more structured and individualized guidelines for follow-up of patients with CRC as well as personalized treatment, based on factors other than resectability as currently defined. *Study II*: A meaningful number of patients with liver metastases were not managed according to best available evidence and the potential for higher resection rates is considerable. *Study III*: The highly selected patients treated with a multiple MWA strategy had a survival benefit compared with patients treated with palliative chemotherapy but the recurrence rate was high. *Study IV*: Sufficient accuracy was achieved using percutaneous MWA with stereotactic navigation.

LIST OF SCIENTIFIC PAPERS

I. **Colorectal cancer liver metastases – a population-based study on incidence, management and survival**
J. Engstrand, H. Nilsson, C. Stömberg, E. Jonas, J. Freedman
(submitted manuscript)

II. **The impact of a liver specific multidisciplinary assessment in patients with colorectal cancer liver metastases – a population-based study**
J. Engstrand, N. Kartalis, C. Strömberg, M. Broberg, A. Stillström, T. Lekberg, E. Jonas, J. Freedman, H. Nilsson
(submitted manuscript)

III. **A multiple microwave ablation strategy in patients with initially unresectable colorectal cancer liver metastases – A safety and feasibility study of a new concept**
Engstrand J, Nilsson H, Jansson A, Isaksson B, Freedman J, Lundell L, Jonas E.
European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2014;**40**(11): 1488-1493

IV. **Stereotactic CT-Guided Percutaneous Microwave Ablation of Liver Tumors With the Use of High-Frequency Jet Ventilation: An accuracy and Procedural Safety Study.**
Engstrand J, Toporek G, Harbut P, Jonas E, Nilsson H, Freedman J.
American Journal of Roentgenology. 2017 Jan;208(1):193-200

CONTENTS

LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
ALPPS	Associated liver partition and portal vein ligation for staged hepatectomy
APC	Adenomatous polyposis coli
ASA	American Society of Anesthesiologists
BCLC	Barcelona clinic liver cancer
BSC	Best supportive care
CEA	Carcinoembryonic antigen
CI	Confidence interval
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CRC	Colorectal cancer
CRCLM	Colorectal cancer liver metastases
CRS	Complete cytoreductive surgery
CT	Computed tomography
DFS	Disease-free survival
DLP	Dose-length product
DW	Diffusion-weighted
EGFR	Epidermal growth factor receptor
EM	Electromagnetic
FLR	Future liver remnant
FOLFIRI	FOL-folinic acid (Leucovorin); F-Fluorouracil (5-FU); IRI-irinotecan (Camptosar)
FOLFOX	FOL-folinic acid (Leucovorin); F-Fluorouracil (5-FU); OX-oxaliplatin (Eloxatin)
Gd-EOB-DTPA-MRI	Gadoxetic acid enhanced magnetic resonance imaging
HAI	Hepatic arterial infusion
HCC	Hepatocellular carcinoma
HFJV	High frequency jet ventilation
HIFU	High-intensity focused ultrasound

HIPEC	Hyperthermic intraperitoneal chemotherapy
HR	Hazard ratio
IR	Infrared
IRE	Irreversible electroporation
IVC	Inferior vena cava
KRAS	Kirsten rat sarcoma viral oncogene homolog
LM	Liver metastases
LTP	Local tumour progression
LV	Leucovorin
MDT	Multidisciplinary team
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MWA	Microwave ablation
OR	Odds ratio
OS	Overall survival
PFS	Progression free survival
PVE	Portal vein embolization
PVL	Portal vein ligation
RECIST	Response evaluation criteria in solid tumours
RFA	Radiofrequency ablation
SBRT	Stereotactic body radiation therapy
SCCR	Swedish Colon Cancer Registry
SEER	Surveillance, Epidemiology and End Results
SIRT	Selective internal radiation therapy
TACE	Transarterial chemoembolization
TPE	Target positioning error
US	Ultrasound

1 INTRODUCTION

1.1 COLORECTAL CANCER

1.1.1 Epidemiology

Colorectal cancer (CRC) is one of the most common malignancies in Western countries. It is the third most common cancer in women (11.3% of all cancer) and the fourth most common cancer in men (10.8% of the total) in Sweden (1). There is a wide geographical variation in the age-standardized incidence of CRC, with a 10-fold difference between high-risk regions (Australia, New Zeeland, Japan and Western countries) and low-risk regions (Africa, India and other parts of southeast Asia) (2). CRC incidence rates have decreased over the years in both males and in females (3). The lifetime risk of CRC in the average person above the age of 50 is 5-6%, that is in a person without a personal or family history of CRC (3). In Sweden, 4000 new cases of colon cancer are diagnosed annually and 2000 new cases of rectal cancer. The incidence of rectal cancer is higher in men and that of colon cancer is slightly higher in women (4).

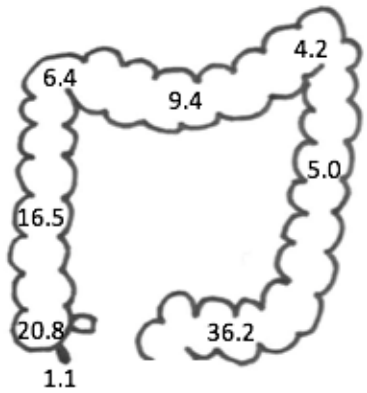


Figure 1. Tumour location of adenocarcinoma of the colon (in percentages), with 0.4% missing data, based on data from the National Cancer Registry of patients diagnosed in Sweden from 2007 to 2011 (5).

Five-year survival has improved over the last few decades and the five-year survival for Swedish patients with colon and rectal cancer diagnosed between 2005-2009 was 61% for men, and 65% and 64% for women, respectively (6). The five-year stage-specific relative survival in colon cancer is presented in **Table 1**. Relative survival rates for rectal cancer were similar to colon cancer (7, 8).

Table 1. Surveillance, Epidemiology and End Results Program data for five-year stage-specific relative survival rates in colon cancers based on sixth edition of the American Joint Committee on Cancer Staging Manual for colon and rectal cancer.

	Stage I	Stage II A	Stage II B	Stage III A	Stage III B	Stage III C	Stage IV
Colon cancer	97.1	87.5	71.5	87.7	75.0 (T1, T2, N2) 68.7 (T3, N1)	47.3 (T3, N2) 50.5 (T4, N1) 27.1 (T4, N2)	11

Values are in percentages

1.1.2 Molecular pathogenesis

1.1.2.1 Progression from adenoma to carcinoma

CRC is a heterogeneous disease with multiple underlying genetic mutations causing different clinical phenotypes. There are two main pathways involved in the progression from adenoma to carcinoma in the colon and rectum, namely the adenoma-carcinoma sequence and the serrated adenoma pathway (9), **Figure 2**. The former conventional pathway accounts for approximately 70 to 80% of all CRCs and is more prevalent in the left colon and rectum. It describes the gradual progression from normal mucosa to adenoma and then to carcinoma due to a series of genetic changes such as mutation and gene amplification. Adenomas typically precede cancer by over 10 years. The serrated adenoma pathway is estimated to account for approximately 10 to 30% of all CRCs (10, 11). Most CRCs arising in the serrated adenoma pathway develop from sessile serrated adenomas of the right colon and are notoriously difficult to recognize. This is thought to in part explain why screening colonoscopy is more effective in preventing left-sided cancer (12).

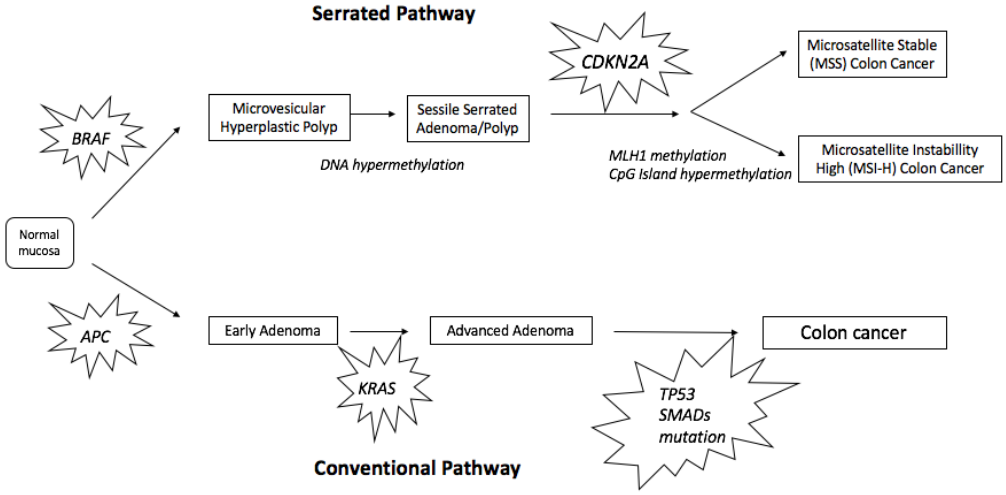


Figure 2. The serrated adenoma and adenoma-carcinoma pathways.

1.1.2.2 Molecular pathways in colorectal cancer progression

Knowledge of specific genetic events that take place in colorectal carcinogenesis may have implications for diagnosis, prognosis and treatment. Lately, research has focused on interactions of hormones, energy balance, intestinal flora and inflammation to explain different epidemiological associations (13). There are three important molecular pathways leading to CRC development, either separately or in combination: 1) *chromosomal instability (CIN),* 2) *microsatellite instability (MSI)* and 3) *CpG island methylator phenotype (CIMP).*

CIN is associated with 65-70% of sporadic CRCs and is characterized by a steadfast increased rate of additions and losses of chromosomal material. This pathway comprises an imbalance in the chromosome number, aneuploidy, and loss of heterozygosity. Responsible for such instability are defects in chromosomal segregation, DNA damage repair and specific mutations in certain oncogenes and tumour suppressor genes. The classical CIN pathway, as

illustrated in **Figure 2,** starts with the acquisition of mutations in the key tumour suppressor gene: adenomatous polyposis coli (APC) gene, followed by the mutational activation of oncogene Kirsten rat sarcoma viral oncogene homolog (KRAS) and the inactivation of the tumour suppressor gene TP53 (14).

MSI occurs because of inactivating mutations in the DNA mismatch repair (MMR) genes that are responsible for correcting DNA replication errors (including *MLH1*, *MSH2* and *MSH6*). It is present in 15% of sporadic CRC cases and is the distinguishing condition in Lynch syndrome. Based on a five-marker MSI panel, tumours with instability in >30% of markers are called MSI-high, those with instability in <30% are called MSI-low and those without microsatellite instability are called MSI stable. MSI tumours are often found in the proximal colon and are characterized by mucinous histology, poor differentiation and lymphatic infiltration (7) but confers a good prognosis (14).

The CIMP pathway, with hypermethylation in the promoter region, results in the transcriptional inactivation of genes that have tumour suppressive roles or are involved in the cell cycle. It is referred to as an epigenetic alteration since it does not change the DNA sequence (14).

1.1.2.3 Molecular markers of prognosis and therapy implications

Mutations in the *BRAF* gene appear to be an early event in the CIMP tumours (serrated pathway), **Figure 2**. *BRAF* mutations are present in 5-10% of patients with CRC. *BRAF* is a protein kinase downstream of RAS in the RAS/RAF/MEK/ERK pathway where the last step controls cell cycle processes. Metastatic *BRAF*-mutated tumours are associated with a poor prognosis when compared with wild-type tumours. The clinical characteristics correlated with this genotype are female gender, older age, right-sided tumours, high-grade features, and MSI-high status (15). *KRAS* is mutated in 30-40% of CRC and induces cell growth by activation of growth factor signal transduction (7).

Identifying biomarkers that predict sensitivity and resistance to chemotherapy is of major clinical importance. Differences have been identified in survival between CRC subtypes based on MSI, CIMP, *BRAF*-mutation and *KRAS*-mutation status. The most favourable survival is seen among patients with MSI-high tumours and the worst survival in tumours with CIMP and *BRAF* mutations (16). First-line treatment of CRC with 5-fluorouracil (5-FU) have been shown to fail in the presence of MSI tumours. Treatment with epidermal growth factor receptor (EGFR) inhibitors is without effect in tumours with codon 12 and 13 mutations in *KRAS,* and *BRAF*-mutated tumours also exhibit resistance to anti-EGFR treatment (7).

1.1.3 Predisposing conditions and risk factors for colorectal cancer

1.1.3.1 Modifiable risk and preventive factors

Overweight and physical inactivity (17), certain types of diets (red and processed meat) (18), smoking (19), heavy alcohol use (20) and diabetes mellitus (21) are established risk factors for CRC, **Table 2**. The exact effects of these risk factors have been difficult to establish and whether they influence the risk differently depending on gender and for development of colon versus rectal tumours. There is emerging evidence that different infectious agents, such as Helicobacter pylori, are associated with an increased risk of CRC (22). Preventive factors established in epidemiological studies are physical activity (23), oral contraceptive use (24), aspirin use (25) and endoscopy with removal of pre-cancerous adenomas (26), **Table 2**.

Table 2. Summary of some preventive factors and risk factors for colorectal cancer.

Factor	Relative risk
Older age	↑↑↑
Family history (first-degree relative)	↑↑
Male gender	↑↑
Inflammatory bowel disease	↑↑
Diabetes	↑
Obesity	↑
Red meat	↑
Smoking	↑
Alcohol	↑
Helicobacter pylori	(↑)
Oral contraceptives	↓
Physical activity	↓
Aspirin	↓
Colonoscopy	↓↓

Parenthesis indicates strong but not fully verified associations

1.1.3.2 Insusceptible risk factors

The single most important risk factor is advanced age and CRC is predominantly a disease of late middle-aged and elderly individuals (27). It is estimated that up to 20% of CRC cases have a familial component but without a clear hereditary disease (28). Individuals with a family history of CRC and colorectal adenoma in a first-degree relative are at increased risk of developing CRC compared with those without such a history. Relative risks are greatest for relatives of patients diagnosed young, (relative risk 3.87) and those with more than one relative with CRC (relative risk 4.25) (29). There is an increased risk of CRC in patients with inflammatory bowel disease but the risk is declining compared with historic cohorts. Hereditary CRC of a syndrome type account for nearly 6% of all cases (7).

1.1.4 Classification of colorectal cancer

Most CRCs are adenocarcinomas (75-80%) followed by mucinous adenocarcinoma (10%) and serrated adenocarcinoma (10%). Tumour grading into high-grade and low-grade is based on the proportion of tumour composed of glands relative to solid areas. The most important predictive factor of tumour behaviour and outcome is the anatomic extent of tumour spread, classified according to the TNM staging system. The TNM classification is divided into three parameters where T describes the primary tumour (**Figure 3**), N the nodal (lymph node) status and M the presence or not of distant metastases (30), **Table 3 and 4**. Other prognostic factors are carcinoembryonic antigen (CEA), tumour deposits, perineural invasion, MSI, tumour regression grade, vessel invasion and extramural vessel invasion (6).

Definition	
Primary tumour (T)	
Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into pericolorectal tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
Regional Lymph Nodes (N)	
Nx	Regional LN cannot be assessed
N0	No regional LN metastasis
N1a	Metastasis in one regional LN
N1b	Metastasis in 2-3 regional LN
N1c	Tumour deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional LN
N2a	Metastasis in 4-6 regional LN
N2b	Metastasis in seven or more regional LN
Distant metastases (M)	
M0	No distant metastasis
M1a	Metastases confined to one organ or site
M1b	Metastases in more than one organ or peritoneum

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

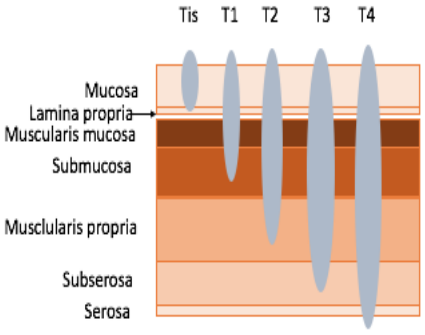


Table 3 (left). TNM-Classification 7th edition for colorectal cancer according to local invasion depth (T-status), lymph node (LN) involvement (N status), and presence of distant metastases (M status). **Table 4 (upper right).** Classification of colorectal cancers according to Union Internationale Contre le Cancer stage (UICC stage) (30). **Figure 3 (bottom right).** Illustration of tumour invasion depth. T1 tumours are sub-classified into sm1, sm2, and sm3, invading the superficial, middle and deep one-thirds of the submucosa, respectively.

1.1.5 Treatment of colorectal cancer

1.1.5.1 Surgical treatment

Radical excision of a colon tumour along with the appropriate vascular pedicle and accompanying lymphatic drainage is the appropriate surgical strategy. Total mesorectal

excision is the optimal surgical treatment for low or mid-rectal cancer (31). Surgical resection is undertaken in all patients unless the tumour is deemed locally unresectable, if there is a medical contraindication to surgery or in patients with asymptomatic primary tumours in the presence of incurable disseminated disease.

1.1.5.2 Chemotherapy

For decades, fluoropyrimidines have been the mainstay of CRC chemotherapy (intravenous 5-FU plus leucovorin [LV] or oral capecitabine [Xeloda]). Since the turn of the century, two new cytotoxic agents have been introduced: a topoisomerase inhibitor named irinotecan (Campto) and oxaliplatin (Eloxatin), a third-generation platinum compound (32). Adjuvant treatment for six months after radical excision of colon cancer reduces the risk of relapse and enhances the chance for long-term survival. In stage III disease, there is a strong evidence base that supports adjuvant chemotherapy (6). A number of risk factors are taken into account in patient selection for adjuvant chemotherapy in stage II colon cancer. Factors that increase the risk of relapse include T4 disease, the presence of vessel invasion, <10 examined lymph nodes, poorly differentiated tumours and emergency surgery. Individuals with MSI-high are at lower risk of relapse, at least in stage II disease. The NSABP C07 study demonstrated that the addition of oxaliplatin to infusional 5-FU/LV resulted in a better five-year disease-free survival (DFS) (33). The MOSAIC trial stated that the absolute improvement in OS for high-risk stage II disease was 1.7% as opposed to 0.1% in low-risk stage II and 4.2% for stage III (34). In summary, adjuvant treatment with 5-FU/leucovorin reduced the relative risk for relapse in stage III disease with 30-40%. When adding oxaliplatin, the relative risk reduction is further increased by 19%. In stage II disease, the relative risk reduction is 20 % with 5-FU/LV and an additional 18% with oxaliplatin (6).

1.1.5.3 Targeted therapy

Cetuximab (Erbitux) and panitumumab (Vectibix) are anti-EGFR antibodies that inhibit downstream signalling of cell growth and proliferation and apoptotic pathways. In patients with *KRAS* mutations, the mutations cause constitutive activation of signalling cascades downstream to EGFR and therefore anti-EGFR therapy is not effective (35). Anti-EGFR treatment has shown clinical benefit only in tumours that are *KRAS* wild-type. Bevacizumab (Avastin), an anti-vascular endothelial growth factor antibody that inhibits soluble protein and results in an anti-angiogenic effect in tumours, is used as a first line therapy in metastatic CRC (36). The combinations of biologic and cytotoxic agents have become the standard of care for the treatment of metastatic CRC but lack proven benefits as adjuvant treatment of primary colon cancer. Two randomized trials, the NSABP C08 and the NO147 trials, assigned patients to FOLFOX with or without bevacizumab and cetuximab, respectively. Both failed to prove significant differences in DFS (37, 38).

1.1.5.4 Radiotherapy

Radiotherapy uses ionising radiation to eliminate cancer cells. The indications for radiation in rectal cancer are to reduce the risk of local recurrence and to shrink locally advanced tumours

to facilitate successful resection. In a Cochrane review it was concluded that pre-operative radiotherapy reduces the risk of local recurrence compared with surgery alone and overall mortality is marginally improved (39). The addition of 5-FU/LV to pre-operative long-course radiotherapy halved the risk of local recurrence but had no impact on overall survival (OS) in two large European phase III trials (40, 41).

1.1.6 Differences between right- and left-sided colon cancer

1.1.6.1 Incidence, survival and clinical presentation

An increasing incidence of right-sided colon cancer has been seen over the last decades. Patients with right-sided tumours are more often females, are slightly older and more often present with advanced (T3/T4) tumours (42). Data from a meta-analysis demonstrated that those with right-sided cancer had a significantly worse prognosis in terms of OS than those with left-sided cancer (43). Patients with right-sided tumours often present with more subtle signs such as microcytic anaemia and weight loss while left-sided typically present with rectal bleeding and alterations in bowel habits (43).

1.1.6.2 Embryology and anatomy

The proximal and distal colon segments are of different embryologic origin. The caecum, ascending colon and proximal two-thirds of the transverse colon originate from the midgut while the remaining segments to the upper anal canal derive from the hindgut. Branches of the superior mesenteric artery supply the proximal colon, while the distal colon gets its blood supply from the inferior mesenteric artery (44). Nearly all venous blood from the colon flows into the portal vein and the liver capillaries are the first capillaries encountered by portal blood-borne cancer cells. A portion of venous blood from the rectum enters the inferior vena cava (IVC) and thus directly reaches the lungs without a liver pass (45).

1.1.6.3 Immunological and molecular differences

There is an increased immune activity in the caecum compared with the rectum and the distal colon and rectum have the highest concentration of microbiota (44). Tumours with CIN are more often found in the hindgut and tumours in the right colon are more often CIMP/MSI/BRAF positive (44).

1.1.6.4 Response to chemotherapy

Right- and left-sided cancers benefit equally from adjuvant FOLFIRI chemotherapy. The benefit gained from adjuvant FOLFOX is superior for left-sided cancers. Cetuximab treatment in KRAS wild-type cancers is inferior for right-sided cancers in terms of PFS (46). Advanced left-sided cancers also benefit more from bevacizumab than advanced right-sided cancers (47).

1.2 LIVER METASTATIC COLORECTAL CANCER

1.2.1 Epidemiology

The incidence of liver metastases ranges between 23.6 and 27.3% in population-based studies (48-51). At diagnosis of CRC, 20-25% of patients have metastatic disease (52), in which liver metastases are present in 14.5-17.7% of patients (50, 51). The incidence of detection of metastases at the time of diagnosis of the primary tumour is rising, probably due to better imaging practices and improved imaging techniques (53). Five- and 10-year cumulative incidences of metachronous metastases are reported to be 14.5-15.1% and 16.9%, respectively (50, 51). Around 85% of liver metastases are diagnosed within one year, 94% within two years and 97.5% within the first three years after diagnosis of the primary CRC (50). Among patients with no recurrence five years after diagnosis, 2.2% developed liver metastases between five and 10 years (54). The incidence of metachronous liver metastases with respect to TNM stage is 3.7% for stage I tumours, 13.3% for stage II and 30.4% for stage III (51). There is no consensus on the definition of synchronous versus metachronous as used in the context of CRCLM, which might explain some of the differences in incidence. The time-point of diagnosis of the primary tumour, the time of operation of the primary tumour and a variation of time intervals related to these time-points have been used. The definition of synchronous detection most commonly used today is the detection of liver metastases either before or during the surgical procedure for the primary tumour (55). Data from Manfredi et al. showed that five-year survival rates were inferior in synchronous liver metastases compared with metachronous detection (3.3% vs. 6.1%), while other studies have reported no significant difference (51). Patients who present with synchronous liver metastases tend to have a more locally advanced primary tumour and present with a greater metastatic burden compared with those who develop metachronous metastases (56).

Liver metastases are more often diagnosed in men, a fact that remains significant after adjustment for age and is thought to be explained by both an actual higher frequency of liver metastases as well as a higher incidence of CRC among men (51, 54). Past studies have reported a higher proportion of liver metastases among younger patients and a tendency to a more advanced TNM stage and significantly longer interval between symptom onset and diagnosis of the primary tumour compared with older patients (51, 57).

Conflicting results exist on whether the site of CRC influences the frequency of liver metastases. In a German study as well as a United States-based study, colon cancer more often caused haematogenous spread to the liver (56, 58). In another study by Lee et al. the extrahepatic recurrence rate was higher in patients with lower rectum cancer, although there was no difference between the hepatic recurrence rates (59). In a Norwegian study, left-sided colon cancer was found to be associated with an increased risk of metastatic spread to the liver (60).

1.2.2 Liver metastatic process and growth pattern

Stephen Paget first described the "seed and soil" hypothesis in 1889 in which the metastatic "seed" preferentially grows in an organ environment that provides a suitable "soil". More recently, the hypothesis has expanded to the concept of "pre-metastatic niche formation". Cellular and molecular changes are thought to occur in target tissue well before tumour cells leave the primary site, rendering the target site susceptible to metastatic cells (61).

The liver metastatic process can be divided into a series of stages (62-64). First, the cancer cells need to *"escape from the primary tumour"*. The new blood vessels developing in the primary tumour during growth, angiogenesis, provide an escape route whereby tumour cells can enter into the vascular system *(intravasation)*, which is the second step. Tumour cells might also enter the blood circulation system indirectly via the lymphatic system. As a third step, the tumour cells need to *"survive in the circulation"*. Once in the circulation, CRC cells bind to and cover themselves with platelets leading to better protection from shear stress and the immune response (65). Circulating metastatic cells can enter the liver via the portal vein or the hepatic artery. *"Avoidance of host defence mechanisms"* is the fourth step. In the liver sinusoids, different cells with anti-tumour activity meet the circulating tumour cells. Kupffer cells are specialized macrophages lining the walls of the sinusoids and Pit cells are large granular lymphocytes with high cytotoxic activity against tumour cells (65). If the cancer cells survive so far, the fifth step is the *"arrest at a new site".* Controversy exists over whether mechanical trappings alone in the sinusoidal vessels or specific interactions with the endothelium are required for the formation of metastases. This is followed by *"extravasation into the tissue"*. Once the tumour cells have reached the new site, the cells must initiate and maintain *"growth"* to first form pre-angiogenic micrometastases and finally macroscopic metastases.

1.2.3 Imaging of liver metastases

Contrast-enhanced computed tomography (CT) scans are routinely used for primary staging and disease surveillance of CRC. The recommended follow-up routines on resected patients in Sweden include, besides CEA, CT chest and abdomen at 12 and 36 months post-operatively (6).

Contrast-enhanced ultrasound (US) is significantly inferior to contrast-enhanced CT for the pre-operative detection of liver metastases (66). The best methods for detection of liver metastases are CT and magnetic resonance imaging (MRI) (67). Superior diagnostic performance with increased accuracy and detection of additional liver metastases are achieved when gadoxetic acid-enhanced MRI (Gd-EOB-DTPA-MRI) is used (68, 69). The combination of diffusion-weighted (DW)-MRI and Gd-EOB-DTPA-MRI has the highest sensitivity for detecting liver metastases on a per-lesion basis (70).

1.2.4 The importance of a liver-specific multidisciplinary team assessment

Ideally, the management and treatment of patients with liver metastases should take place in a specialist hepato-pancreato-biliary centre or as part of a network with established referral routines to a specialist centre. The importance of discussing patients with liver metastatic disease at a specialist hepatobiliary multidisciplinary team (MDT) meeting has been demonstrated in several observational studies (71, 72). To qualify as a liver MDT, a hepatobiliary surgeon and an oncologist and a radiologist specialised in liver should participate. Since the use of ablative treatment is increasing, an interventional radiologist or surgeon should also be present (73). Discussion at a liver MDT is associated with higher resection rates (74) and improved DFS (75) and OS (72, 76). Unfortunately, patients that may benefit from resection are not always properly referred (71). There are known discrepancies between medical oncologists and surgeons in assessing resectability and indications for pre-operative chemotherapy (77-79). Some physicians and medical oncologists still judge bilateral disease and large tumour size as contraindications for surgery (80). A difference in referral rates between hospitals in the same region has been reported (74, 81), with data suggesting that a lower referral rate is followed by a lower resection rate and, consequently, a lower survival rate than could ultimately be achieved (48, 74, 81). Moreover, practice patterns related to defining resectable CRCLM and the utilization of curative therapy vary significantly between hospitals (82, 83).

1.2.5 Prognostic factors in colorectal cancer liver metastases

In 1999, Fong and colleagues proposed a clinical risk score for predicting recurrence after hepatic resection for CRCLM based on five clinical criteria: nodal status of the primary tumour, disease-free interval from the diagnosis of the primary tumour to the discovery of the liver metastases of <12 months, number of tumours >1, pre-operative CEA level >200 ng/ml, and the size of the largest tumour >5cm (84). Major improvements in surgical technique and perioperative management of the patient, as well as the introduction of modern chemotherapy have potentially made the scoring system out-dated. A more simplified scoring system for disease-specific survival and recurrence after R0 resection was proposed by Settmacher in 2011. Patients with an extrahepatic tumour at the time of liver surgery are considered as high risk, as are patients with one of the two following factors: N2 of primary tumour or more than two liver metastases (85). All other patients are regarded as low risk. The number of liver metastases is one of the most used predictive factors and the cut-off for considering the patient to have a worse prognosis varies between >1 and >7 lesions. The size of the largest metastasis is also frequently used as a prognostic marker with the cut-off usually being set at 5 cm. The presence of extrahepatic disease is regarded as a factor associated with worse survival and has up until recently been considered as a contraindication to surgery (73). RAS mutations (*KRAS* and *NRAS*) have been shown to be independent predictors of poor OS and DFS as well as being associated with a higher recurrence risk in patients undergoing surgery for CRCLM (86).

Progression on systemic therapy is considered a poor prognostic factor that could exclude a patient from curative-intended liver resection. In patients with potentially resectable metastases, the goal has often been to achieve a high response rate as assessed by the RECIST (response evaluation criteria in solid tumours) criteria in order to convert unresectable metastases to technically resectable metastases (87). Since the introduction of biologic agents that mainly have a cytostatic effect, the relevance of the RECIST criteria has been questioned and the addition of non-sized based morphologic response criteria has been proposed (88, 89). Several studies have described both weak associations between RECIST and pathologic response to chemotherapy and the absence of associations between RECIST response and long-term outcomes (90, 91).

1.3 TREATMENT OF COLORECTAL LIVER METASTASES

1.3.1 Liver anatomy and function

The liver is the largest solid organ in the human body and has a unique dual blood supply. Twenty-five percent of the supply originates from the hepatic artery and 75% from the portal vein. Oxygen-rich blood from the hepatic artery and the nutrient-rich blood from the portal vein is mixed in the hepatic sinusoids before leaving the liver through the hepatic veins that ultimately coalesce into three hepatic veins that drain into the inferior vena cava (IVC) (92).

The liver performs several essential tasks including ammonia detoxification, urea synthesis, protein synthesis and breakdown, bile synthesis and secretion, gluconeogenesis and detoxification of drugs, bacteria and bacterial toxins. For most functions the capacity of the liver exceeds the daily need (31).

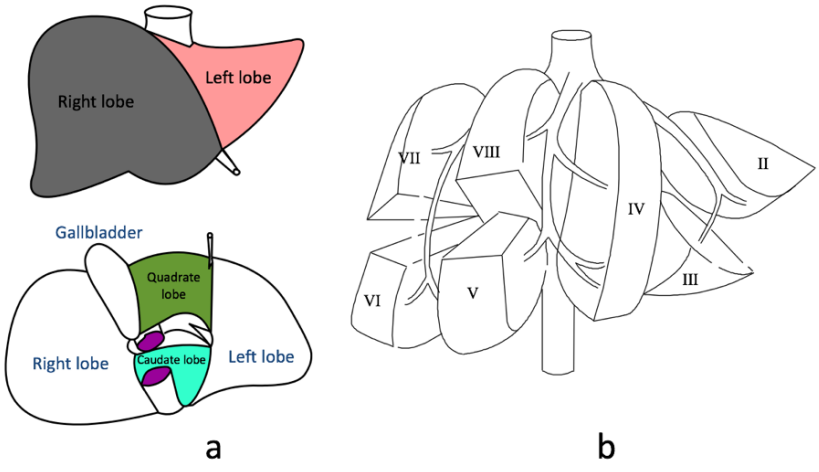


Figure 4: An overview of morphologic (a) and functional (b) anatomy of the liver. Segment I is not visible in this drawing, but located behind Segment IV in front of the inferior vena cava. (*from* Jonas E. Imaging-based liver function testing, Karolinska Institutet 2002; with kind permission)

The classification of liver anatomy according to Couinaud divides the liver into eight functionally independent segments, each with its own blood supply and biliary and venous drainage (93), **Figure 4.** The right and left hemi-livers are separated by the middle hepatic vein in a plane running from the IVC to the gallbladder fossa (Cantlie's line). The right hemi-

liver is divided into anterior (segments V and VIII) and posterior (segments VI and VII) sections by the right hepatic vein (94). The falciform ligament/ligament teres and the umbilical fissure serve as landmarks of the division of the left hemi-liver into a medial section (segment IV, subdivided in segments IVa and IVb) and a lateral section (segments II and III). The plane between these two sections is occupied by the vertical portion of the left portal vein. The plane between the superior and inferior segments is approximately on the level of the portal bifurcation (92), as illustrated in **Figure 4.**

The remarkable capacity of the liver to regenerate makes resections of up to 75% of the liver parenchyma feasible. The future liver remnant (FLR) would then be sufficient for maintenance of post-operative function and regeneration on condition that there is no underlying liver dysfunction. Within 6-8 weeks following major resection, the liver will regain its original volume. Three key factors coexist that facilitate liver regeneration, namely the ability of differentiated hepatocytes to proliferate, the inhibition of processes connecting injury to programmed cell death and alterations in the microenvironment of the liver cells supporting growth (31). If cirrhosis, fibrosis or ongoing liver injury such as biliary obstruction or sepsis is present, liver regeneration might be impaired. Chemotherapy-associated liver changes mainly occur in patients treated with oxaliplatin or irinotecan. The influence of the sinusoidal obstruction syndrome ("blue liver") caused by oxaliplatin-based chemotherapy on outcome after liver resection was reviewed in a recent meta-analysis. It showed no significant effect on short-term outcome (95). Chemotherapy-associated steatohepatitis related to irinotecan treatment, especially in obese patients, has been shown to increase morbidity and 90-day mortality after resection (96). Estimating the function of the FLR has proven difficult since there is a poor correlation between volume and function, especially in diseased livers (97). Peri- and intraoperative conditions such as prior chemotherapy, pre-existing steatosis, oxidative stress and ischaemia/reperfusion injury, most likely compromise function of the FLR.

1.3.2 Liver resection rate trends over time

The number of patients amenable for resection of CRCLM has increased dramatically over recent years due to expanding indications, major surgical and oncological advances and the concept of multimodality treatment (73). The majority of publications addressing treatment of CRCLM come from high volume centres and may not be representative of practice in general. In a Swedish population-based study, Sjövall et al. reported a resection rate of 4% among all patients with detected liver metastases during the time period of 1996-2001 (48). Similarly, Cummings et al. published a resection rate of 6.1% between 1991-2001 (98). The proportion of patients who had surgical resection was higher in a French study by Leporrier et al.: 17.3% between 1994-2002 (49). The resection rate has continued to increase and in a recent study on surgical management among patients with CRCLM, 26.2% of patients underwent resection (2002-2012) (50).

1.3.3 Factors influencing surgical resection rate

Patients with CRC and a high socioeconomic status have more favourable surgical treatment characteristics than patients with a low socioeconomic status (99). Socioeconomic status also influences the likelihood of liver resection, where the socioeconomically favoured population are resected to a greater extent (100). In a large population-based series on surgical management and outcomes of patients with CRCLM, women, older patients and those who resided in the most socioeconomically deprived areas were significantly less likely to undergo surgical resection (101). In two Swedish nationwide studies, inequalities in surgical resection rates were demonstrated where married patients were more likely to have their liver metastases resected. It was also found that for female patients with rectal cancer civil status, education and level of income were all more important than age in the selection for liver surgery (102). In the second study on patients with synchronously detected liver metastases, females and patients treated outside of university hospitals were less likely to undergo liver resection (103). Other known factors associated with a lower probability to undergo a hepatic resection are old age, co-morbid disease, a high number of liver metastases, synchronous liver metastases and the presence of extrahepatic disease (101, 103).

1.3.4 Criteria for surgical resection and long-term survival

Historically, the prognosis of patients with CRCLM not treated with either chemotherapy or surgery was exceptionally poor, with a median survival of 5-10 months. Surgical resection of CRCLM is a potentially curative treatment with currently reported five-year survival rates of 20-58% (54, 87, 104-107) and 10-year survival rates of 22-23% (84, 104, 108). In data published from single large academic institutions five-year survival rates of 64% are reached (109). In population-based materials, 10-year OS range from 4.6 to 15.1% depending on number of liver metastases and surgical resection (50). Ten-year relative survival rates as high as 34% have been reported (54). An actual 10-year cure rate is documented in one of six resected patients (110). When evaluating patients for surgery, both oncological and technical operative factors should be considered. Current technical contraindications to liver resection include the inability to achieve a R0 resection with >25-30% FLR and the presence of unresectable extrahepatic disease, as outlined in **Table 5** (73, 111, 112).

Table 5. Contraindications to liver resection in patients with liver metastases

Category	Contraindication
Technical (A)	
1) Absolute	Impossibility of R0 resection with >30% liver remnant. Presence of unresectable extrahepatic metastases.
2) Relative	R0 resection possible only with complex procedure. R1 resection
Oncological (B)	
1	Concomitant extrahepatic disease (unresectable)
2	Number of lesions >5
3	Tumour progression

Adapted from Adam et al. (111). Patients should be categorised as A1 or A2/B1, B2 or B3.

Potential cure can be achieved in a fraction of patients after R1 liver resection (113). In the era of modern chemotherapy regimens, tumour biology is speculated to be a more important factor in survival than surgical margin, suggesting that the risk of an R1 resection should not be considered as a contraindication to surgery (114, 115).

Extrahepatic disease is not an absolute contraindication to resection with five and 10-year OS of 28% and 10%, respectively. Liver resection, when complete resection of extrahepatic disease is possible, has proven safe and long-term survival can be achieved in spite of disease recurrence in the majority of patients and a true cure is rare (116-119).

A large number of liver metastases should not be a contraindication to curative-intended treatment as resection of multiple bilateral liver metastases as well as multiple thermal ablation of initially unresectable metastases have demonstrated a survival benefit (109). Also, age is not a contraindication even though long-term outcomes are inferior compared with younger patients. Nevertheless, in a substantial proportion of elderly patients, long-term survival will be achieved (120, 121).

The presence of resectable lung metastases is neither a poor prognostic factor nor a contraindication to resection of liver metastases and similar OS is reported for patients who underwent resection of liver and lung metastases and those who had undergone removal of isolated liver metastases leaving the lung metastases in situ (122, 123).

1.3.5 Resectable liver metastases

As illustrated in **Figure 5,** both surgery upfront and perioperative chemotherapy are options in patients presenting with technically resectable liver metastases and favourable oncological criteria. No clear recommendation exists since the EPOC study on perioperative chemotherapy failed to show a major advantage in five-year OS in the group treated with perioperative chemotherapy versus surgery-only, 51% versus 48%, respectively (124). However, based on the same trial, if adverse prognostic factors are present, perioperative chemotherapy is recommended with three months pre-operative FOLFOX (or capecitabine with oxaliplatin) and three months postoperative chemotherapy using the same regime. This has shown to result in an 8% increase in PFS after three years. The New EPOC trial that investigated the possible benefit of adding anti-EGFR treatment to FOLFOX in the neo-adjuvant setting showed a shorter PFS for combination therapy and this combination is not to be used in this setting (125).

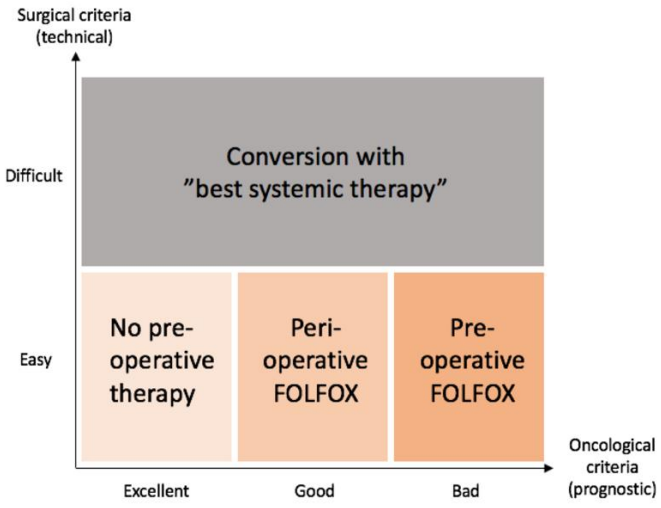


Figure 5. Categorization of patients according to technical and oncological criteria. FOLFOX infusional 5-fluorouracil, leucovorin, oxaliplatin. (Reproduce from Van Cutsem et al. (73))

An increased surgical morbidity with neo-adjuvant treatment was demonstrated in both studies. In patients with more unfavourable prognostic factors, no evidence for best treatment strategy exists, and FOLFOX or a chemotherapy doublet plus monoclonal antibody therapy can be considered (73). **Figure 5** illustrates the proposed categorization of patients into groups based on surgical and oncological criteria and the suggested treatment regimens (73).

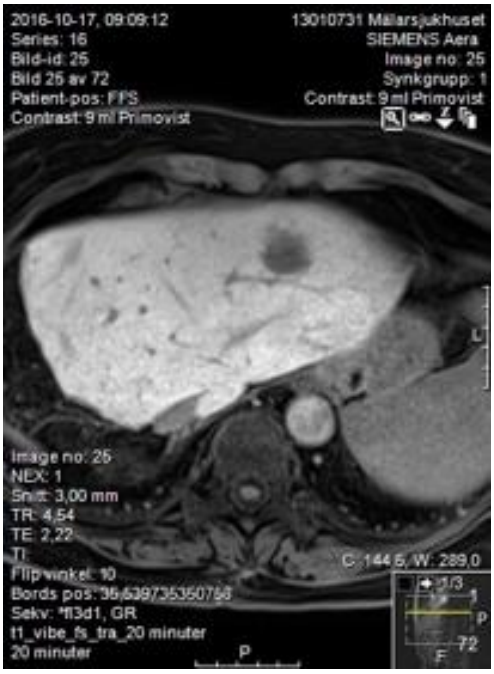


Figure 6. Case illustration 1.

64-year old woman with resected colon cancer who presented with synchronous liver metastases and underwent right hemihepatectomy and surgery of the primary. Six months later, an additional liver metastasis was detected between segments two and three, superficially, measuring 3 cm. Repeated resection was completed and the patient is recurrence free at one-year follow up.

1.3.5.1 Recurrence after liver resection

The recurrence rate following curative-intended surgery is reported to be 56.7-63% within two years (85), and 93% of recurrences are found to occur within the first five years of follow-up (108). The first unique site of recurrence is the liver (45%), followed by lung metastases (18%), liver and extrahepatic metastases (14%), other metastases (14%), and loco-regional recurrence only (9%) (85). Time to recurrence in the liver is correlated with synchronous detection, the number of lesions, R status and American Society of Anaesthesiologists (ASA) score (126). If recurrence occurs after curative resection of liver metastases, repeat hepatectomy for additional liver metastases should be considered and results in survival benefit equal to that of a first resection (127).

1.3.6 Potentially resectable liver metastases

Conversion therapy is given to patients with potentially resectable liver metastases with the aim to transfer technically unresectable liver metastases into a resectable state. In patients with initially unresectable disease, chemotherapy can convert up to 20% of patients to resectability (73, 128). Survival is slightly impaired in the patient category undergoing conversion therapy followed by surgery compared to initially resectable disease but it is still considerably better than if resection is not to be carried out (129). It also seems as if converted patients suffer from earlier liver recurrence (130). Significant increased resection rates were seen in the CRYSTAL and OPUS trials after treatment with FOLFIRI and FOLFOX, respectively, combined with cetuximab (131, 132). Patients with technically unresectable and/or >5 liver metastases were included in the CELIM trial and treated with

either FOLFOX plus cetiximab or FOLFIRI with cetuximab. Encouraging resection rates of 40-43% were achieved across the two treatment arms (133). This was followed by the European phase II OLIVIA trial, where patients with unresectable liver metastases were randomised to an intense arm, FOLFOXIRI plus bevacizumab or a conventional arm, FOLFOX plus bevacizumab. The intense arm was associated with both higher response and resection rates (134). In a systematic review of patients with initially unresectable liver metastases who underwent systemic chemotherapy, 22.5% had a curative resection and a median survival time of 45 months (135). A nomogram to predict survival after hepatectomy in patients with initially unresectable liver metastases who underwent conversion therapy was recently presented by Adam and colleagues. Five independent prognostic factors for survival were identified, namely node-positive primary, tumour number at hepatectomy > 6, carbohydrate antigen 19-9 level at hepatectomy > 37 units/ml, disease progression during first-line chemotherapy and presence of concomitant extraheptic disease (136).

In patients in need of tumour shrinkage, molecular profiling is essential in determining further treatment, **Figure 7**. After the administration of conversion therapy, an evaluation of resectability should be conducted every two months.

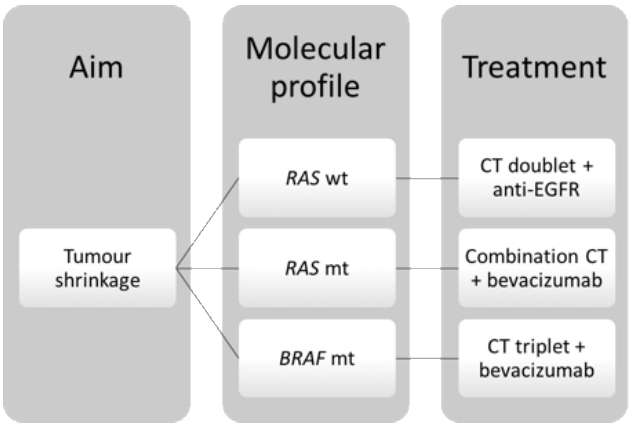


Figure 7. Treatment algorithm for tumours in need of shrinkage and conversion to resectable disease**.** Wild-type (wt). Mutation (mt). Chemotherapy (CT).

1.3.7 Surgical strategies to improve resectability

1.3.7.1 Portal vein occlusion

Portal vein embolization (PVE) or portal vein ligation (PVL) induces atrophy of the liver to be resected and hypertrophy of the liver that will constitute the FLR and is used in patients with a marginal FLR to prevent post-resection liver failure and death. In a meta-analysis of articles on the impact of PVE on liver resection, 85% of patients underwent the intended hepatectomy after PVE (137). In performing PVE, the portal vein can be accessed either by a percutaneous transhepatic approach, that is most commonly used, or via the ileocolic vessels. In a meta-analysis results of PVE and PVL were comparable in terms of percentage increases in the FLR, morbidity and mortality (138).

1.3.7.2 Two-stage hepatectomy

A lesser resection of metastases in the FLR and PVE or PVL during surgery is followed by the major hepatectomy when volume manipulation has resulted in a sufficient FLR. In patients with bilateral disease, an alternative is a single-stage procedure with a combination of local ablation that results in survival rates similar to two-stage hepatectomy but with less overall morbidity (139).

1.3.7.3 Associating liver partition and portal vein ligation for staged hepatectomy

Sufficient FLR hyperthrophy after portal vein occlusion is not always achieved. There is furthermore the risk of tumour progression during the 3-5 week waiting period that may preclude further surgery (140). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) was first published by Schnitzbauer et al. in 2012 (141). Briefly, at a first operation the liver parenchyma is transected in the intended resection plane and PVL of the liver to be resected is performed. During the initial procedure, any tumours in the FLR can be removed by resection or ablation. Once sufficient hyperthrophy of the FLR is achieved, the deportalized liver is resected at a second operation (142). It is recommended that the CT for volumetry after step one should be done 8-10 days after the first operation and repeated weekly for four weeks if the FLR is insufficient (143). The rapid regeneration achieved with the ALPPS procedure is probably multifactorial, including redistribution of portal blood by the PVL, interruption of intrahepatic portal collaterals with parenchyma transection and induction of an inflammatory response with the release of growth factors. Part of the previous paradigm for liver surgery, namely that the FLR must consist of two continuous segments, was challenged by the introduction of monosegment ALPPS, basing the FLR on only one Couinaud segment (144). ALPPS has been demonstrated to offer a higher rate of complete resection in patients with primarily unresectable liver tumours compared with conventional staged hepatectomies but with a higher mortality (145). A meta-analysis published in 2015 with data from 295 patients revealed a 90-day mortality of 11% and Clavien-Dindo complication grade IIIa or higher occurred in 44% of patients (146). Proper oncological results of this procedure are lacking. Intermediate oncological results were investigated by Björnsson and colleagues and the estimated two-year OS was 59% from surgery and 73% from diagnosis of liver metastases. In a subsequent study, the OS, rate of severe complications and perioperative mortality were comparable with two-stage hepatectomy (147).

1.3.7.4 Ablative treatment

For patients with metastases unfavourably positioned for resection or with a large number of metastases, ablative treatment can be used in combination with systemic therapy and resection, **Figure 8.**

1.3.7.5 Thermal ablation

Thermal ablation such as radiofrequency ablation (RFA) and microwave ablation (MWA) has been used for some years with data supporting its safety and efficacy. This is elaborated on in chapter 1.5. The CLOCC trial was the first randomized study on the efficacy of RFA in unresectable liver metastases. Difficulties in patient recruitment resulted in premature closure of the trial with the result that the study did not achieve sufficient power to demonstrate a significant result for its primary end-point of OS. In fact, there was no difference in 30-month OS between RFA plus chemotherapy versus chemotherapy alone (61.7% versus 57.6%, respectively) but a significantly improved three-year PFS was seen (27.6% versus 10.7%, respectively) (148).

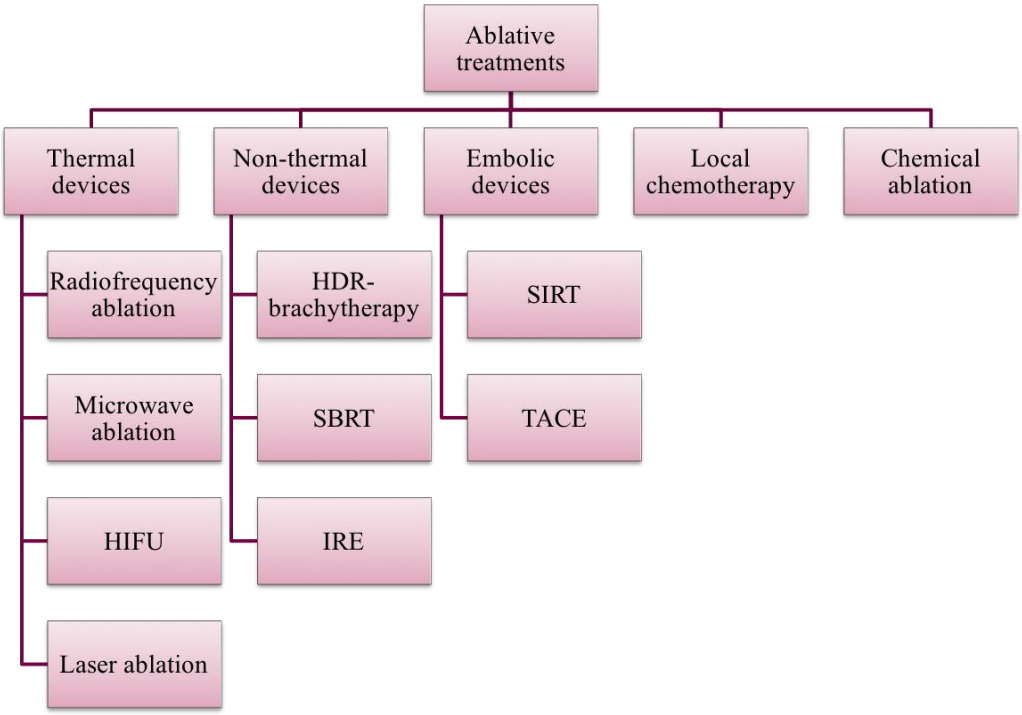


Figure 8. Flow-chart of different ablative treatment modalities for CRCLM. High-dose-rate (HDR)-brachytherapy. Stereotactic body radiation therapy (SBRT). Irreversible electroporation (IRE). Selective internal radiation therapy (SIRT). Transarterial chemoembolization (TACE). High-intensity focused ultrasound (HIFU).

1.3.7.6 High-dose-rate brachytherapy

High-dose-rate brachytherapy does not have the limitations inherent to thermal ablation techniques. However, CRC tumour cells seem less sensitive to radiation compared with hepatocellular carcinoma (HCC) cells, hence the technique is not as commonly used in the multimodality treatment of liver metastases. One or multiple co-axial catheters are inserted using image-guidance, followed by treatment planning and single fractionated high dose irradiation (149).

1.3.7.7 Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is defined as a method of external beam irradiation (photons or particles) that accurately delivers a high dose of irradiation in one or

few fractions to an extracranial target. SBRT has been reported to achieve high local control rates, similar to that of RFA in unresectable oligometastatic disease (150).

1.3.7.8 Irreversible electroporation

Irreversible electroporation (IRE) is increasingly used in patients with tumours close to the portal triad or large vessels where thermal ablation is considered less effective and potentially harmful. High-voltage electrical pulses are delivered through precisely placed parallel electrodes causing innumerable permanent nanopores in the cell membrane that disrupt cellular homeostasis and cell death follows (151). The capability of IRE to preserve vital structures, such as arteries, veins and intrahepatic bile ducts, is explained by the fact that cell death is mediated by apoptosis through disruption of the cell membrane and since vascular elastic and collagenous structures are mainly formed by proteins, such structures are not damaged by IRE ablation (152). Published local control rates are inferior to thermal ablation, ranging from 55-93% with a median follow-up below one year (153-155).

1.3.7.9 Selective internal radiation therapy

Selective internal radiation therapy (SIRT), also called radioembolization, is used as salvage therapy for patients with unresectable liver metastases. Microspheres containing yttrium-90 are permanently implanted into the liver tumour via the hepatic artery. Radiation is delivered within a small range from the microsphere (2.5 mm) and therefore spares adjacent normal liver tissue (156). A review of the role of SIRT concluded that there is no evidence that SIRT improves survival or quality of life in CRCLM (157). SIRFLOX was a randomized trial investigating the efficacy of adding SIRT to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver-only metastases. The addition of SIRT did not improve PFS but delayed disease progression in the liver (158).

1.3.7.10 Transarterial chemoembolization

In transarterial chemoembolization (TACE), one or more chemotherapeutic drugs and embolic materials are injected into the hepatic artery. The method is most suitable for hypervascular tumours. A strong cytotoxic and ischaemic effect is achieved after the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumour-feeding blood vessels. The embolic material reduces the blood flow and prolongs tumour exposure to the chemotherapeutic agents. In a propensity score matching study, no significant differences in OS were seen in patients with unresectable liver metastases treated with or without TACE (159).

1.3.7.11 Hepatic arterial infusion

With hepatic arterial infusion (HAI) therapy, chemotherapy is delivered through the hepatic artery and is based on the principle that CRCLM are mainly supplied by arterial neovascularization via the hepatic artery, whereas healthy liver parenchyma is supplied by a mixture of 25% arterial and 75% portal blood. The administration of drugs with a high first-pass effect that rapidly metabolize in the liver allows for a high concentration of active drug

in the liver. In patients with liver metastases refractory to standard chemotherapy, a response to HAI resulting in anti-tumour activity with conversion to resectability and improvement in survival can be achieved (160, 161).

1.3.7.12 High-intensity focused ultrasound

High-intensity focused ultrasound (HIFU) is emerging as a minimally invasive treatment option for patients with HCC and CRCLM. It can be used both for thermal (coagulative necrosis) and mechanical destruction (subcellular fragmentation) of tissue. It uses acoustic lenses or curved piezoelectric transducers to focus beams of US on a target located deep in the body. Potential applications and its role in the treatment algorithms of HCC and metastatic disease are not yet determined (162). Complications related to the procedure are skin burns at the application site and osteonecrosis of ribs or vertebra along the US pathway (163).

1.3.7.13 Liver transplantation for secondary tumours

Liver transplantation for patients with unresectable liver-limited liver metastases has been performed with five-year OS of 60% (164). However, all patients reported in the Norwegian study experienced recurrence (165).

1.3.8 Unlikely to become resectable metastases

Patients with technically never resectable metastases are a heterogeneous group where tumour- and disease-related symptoms and patient-related factors determine the intensity of chemotherapy or alternatively best supportive care.

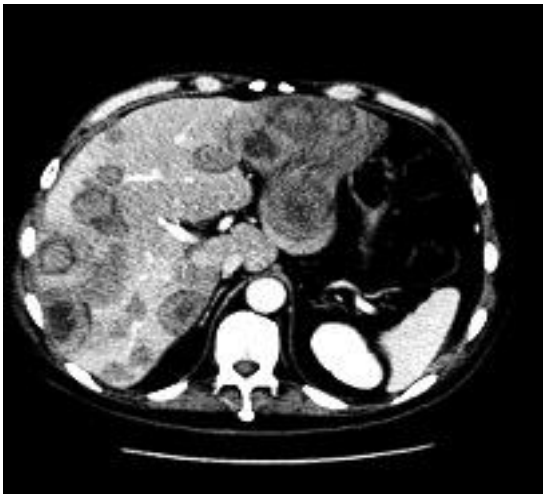
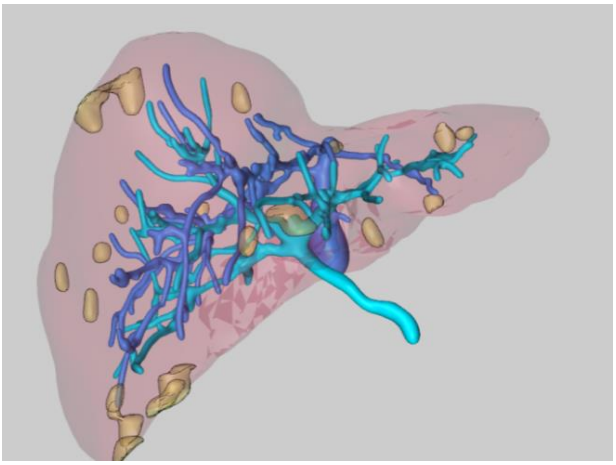


Figure 9. Case illustration 2

55-year old male presenting with diffuse abdominal pain. On colonoscopy, a tumour is identified in the ileocecal valve. On imaging, metastases in the abdominal wall, adrenal glands, peritoneal carcinomatosis and multiple, bilateral liver metastases are detected. After multidisciplinary assessment, the patient was considered unresectable.



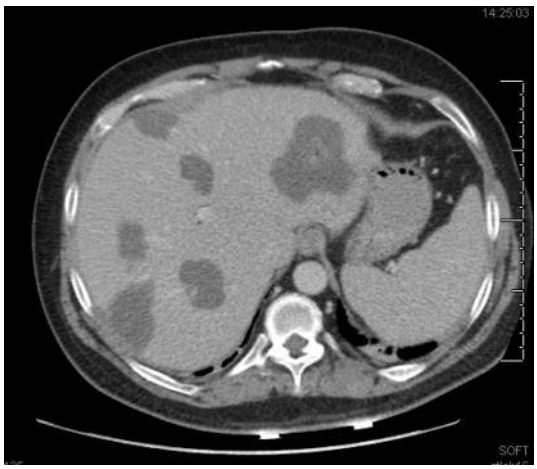


Figure 10 A (above left) and B (above right). **Case illustration 3**:

48-year old male presenting with acute colon obstruction treated by emergency colostomy. Further imaging and colonoscopy revealed an adenocarcinoma of the left colon flexure and widespread liver disease. On multidisciplinary assessment, palliative chemotherapy was initiated. On imaging evaluation, a remarkably good response was noted and the patient was referred to a liver MDT for further assessment and the strategy was changed to curative intention. The patient underwent simultaneous resection of the primary tumour and open microwave ablation of 22 liver metastases including vanished lesions. Recurrence was detected four months later and after additional chemotherapy, right hemi-hepatectomy and re-ablation was performed. Figure 10 A (above left) MeVis (MeVis Medical Soulutions) reconstruction of liver with multiple tumours visible. Figure 10 B (above right): Post-ablation CT-scan.

1.3.9 Different approaches in synchronous liver metastatic colorectal cancer

If a patient presents with synchronously detected resectable liver metastases, there are three potential options in proceeding with resection, namely synchronous resection of liver and bowel tumours, surgery of the primary first or liver-first resection. The decision in favour of a specific strategy is dependent on the risk of complications related to the first procedure, anatomic location of the tumour, obstructive or anaemic symptoms from the primary tumour, patient comorbidity and the requirement of neo-adjuvant chemotherapy and conversion chemotherapy (52). A systematic review of articles comparing synchronous surgery with sequential bowel-first or liver-first approaches provides support for the continued use of all three options and similar survival in the three groups is reported (166).

1.3.10 Resection of extrahepatic disease with concomitant liver metastases

In a systematic review that reported on 3481 patients from 50 studies, addressing the role of surgery for extrahepatic disease in the presence of resectable liver metastases, a median OS of 31 months (range 9-98 months) was found (167). Findings that OS was significantly better for patients who had complete liver surgery without resection of extrahepatic disease than those in whom liver surgery was not completed suggest that prolonged survival is possible by performing a hepatectomy and leaving extrahepatic disease in situ (136). In a study based on data from LiverMetSurvey, an international internet-based registry analysing outcomes following liver resection for CRCLM, patients with resectable liver- and lung metastases had

similar survival to patients who underwent surgery for liver only metastases (123). In a meta-analysis reporting on OS after resection for liver metastases in the presence of extrahepatic disease, five-year OS was 26% for lung metastases, 17% for peritoneal metastases and 15% for lymph node metastases (168).

1.3.11 Management of disappearing liver metastases

Disappearing liver metastases refers to the inability to detect metastasis after the administration of pre-operative chemotherapy on imaging (complete radiological response), at exploration (complete clinical response) or in the resected liver (complete pathological response). Complete radiological response occurs in 5-37% of patients (169). Complete radiological response does not necessarily imply a complete clinical response and residual macroscopic disease is found in 25-45% at time of operation (170). Not resecting disappearing liver metastases is associated with an increased risk of intrahepatic recurrence but with no significant effect on OS (171). Microscopically residual disease was found in up to 80% of patients when the area of the disappearing liver metastases was included in the resection specimen (172). Management of disappearing liver metastases is controversial and possible strategies include a chemotherapy break before surgery since some disappearing liver metastases recur quickly, chemotherapy alone, resection with or without ablation or HAI therapy or resection followed by additional adjuvant chemotherapy. The current recommendation is that the liver resection should include the sites of disappearing liver metastases (170).

1.4 EXTRAHEPATIC METASTASES IN COLORECTAL CANCER

1.4.1 Lung metastases

The lungs are the second most common site of metastasis and lung metastases occur in 10-20% of patients with CRC (173, 174). The indications for pulmonary metastasectomy, established by the National Comprehensive Cancer Network Guidelines Version 2.2016 are as follows: 1) complete resection possible with maintenance of adequate lung function, 2) the primary tumour is R0 resected, 3) resectable extrapulmonary metastases do not preclude resection, 4) re-resection can be considered in selected patients, and 5) ablative techniques can be considered (175). A pre-operative CT is performed since it has a higher sensitivity than both chest x-ray and positron emission tomography for metastases < 1 cm. The specificity is however not equally high. In a systematic review of 5873 patients, 9% had indeterminate pulmonary nodules at chest CT of which 10.8% turned out to be metastases at follow-up (176).

The surgical approach has developed from thoracotomy with lobectomy to more minimally invasive surgery with parenchyma-sparing procedures, such as wedge resection, precision excision, and segmentectomy during video-assisted thoracic surgery (177). The use of RFA as a treatment option for small metastases is appealing because of less reduction of lung

volume after treatment and the percutaneous approach with expected low morbidity (178). In a systematic review of eight articles including 906 patients, using percutaneous RFA for treatment of lung metastases, the five-year OS was 20-54% and DFS of 20-70% (179). However, these patients were highly selected and no cohorts exist for an adequate comparison.

Most studies on pulmonary metastasectomy for lung metastases are retrospective, single-centre reports from a time period reaching back over 20 years and are naturally afflicted by heterogeneous selection criteria with no regard to recent improvements in chemotherapy options. Outcome after pulmonary metastasectomy was assessed in a systematic review and meta-analysis including a total of 2925 patients and reported five-year OS ranged from 27-68% (180).

Factors associated with poor prognosis after pulmonary metastasectomy are mediastinal lymph node metastases, high CEA levels, higher number and larger size of lesions, central location and short disease-free interval (181). The reported recurrence rate after pulmonary metastasectomy is as high as 68% and most likely represents residual nodules that were too small to be detected prior to the resection or occult micrometastases disseminated from extrapulmonary organs. Multiple repeated resections of lung metastases have been demonstrated to be safe and effective with five-year OS after second and third resections being 79% and 78%, respectively (182). Multiple metastatic lung nodules are a strong predictor for poor outcome, but even patients with five or more lesions show an acceptable survival outcome with a five-year OS of 31% (177).

1.4.2 Peritoneal metastases

Peritoneal carcinomatosis is diagnosed in 7-13% (183) of patients with CRC and in approximately 25% of these patients the peritoneum is the only site of metastases (184). Macroscopic complete cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) may provide prolonged survival in selected patients and is now an accepted standard treatment approach. Patients treated without CRS and with systemic chemotherapy only, have a median survival of 12.7 months (185). In two retrospective multi-institutional studies and in one prospective study, CRS plus HIPEC resulted in a median OS ranging from 32 to 45 months with corresponding five-year OS of 35-45% (186-188). The outcome depends on the extent of peritoneal dissemination and is scored using the peritoneal cancer index. A peritoneal cancer index <20, good performance status, postoperative chemotherapy and no synchronous liver metastases are factors associated with improved survival. Involvement of the lower ilium is a negative prognostic factor (6). Synchronous liver metastases were previously considered as a relative contraindication to CRS with HIPEC but more recent studies have shown similar results to that provided for patients with peritoneal carcinomatosis alone (189). CRS followed by HIPEC is performed at the expense of high morbidity and mortality, ranging from 12-52% and 0.9-5.8%, respectively (190).

1.4.3 Other distant metastases

Distant lymph node metastases are found in 3% of patients, depending on regional lymph node involvement. Para-aortic lymph node metastases occur in up to 2% and resection can be performed with minimal morbidity and achieves a survival advantage compared with palliative chemotherapy (191).

Brain metastases are detected in 0.5 to 3.2% of patients with CRC (58, 192) and are associated with younger age, lung metastases (concomitant in 55-85%), rectal primary and *KRAS* mutation (192, 193). Treatment of patients with isolated or symptomatic brain metastases can prolong survival with a reported median survival of 7.6 months after brain surgery if the patients received postsurgical radiotherapy (194). Treatment options include neurosurgery, whole brain external radiotherapy, stereotactic radiosurgery and systemic chemotherapy either alone or in combination.

Bone metastases are detected in 1.5-11%, with a seemingly increasing incidence, possibly due to the expanding role of positron emission tomography scan and overall prolonged survival (58, 195). The management of skeletal metastases is usually palliative and involves the combination of surgery, chemotherapy and radiotherapy for painful lesions. Ovarian metastases are thought to occur in 5-10% of all women with metastatic cancer. It affects younger women more frequently, is associated with a reduced median survival of 19-27 months after detection and is linked to a poor response to chemotherapy (196). Metastases in the kidneys are considered to be extremely rare. In an autopsy report from 1979, 2.7% were found to have metastases in the kidneys (197). A more recent autopsy report described an incidence of 2%-7% for kidney metastases and 5%-16% for adrenal gland metastases (198). Other rare locations for distant metastases are the spleen and pancreas with reported incidences of 1%-2.8% and 1.0-2.6%, respectively (198).

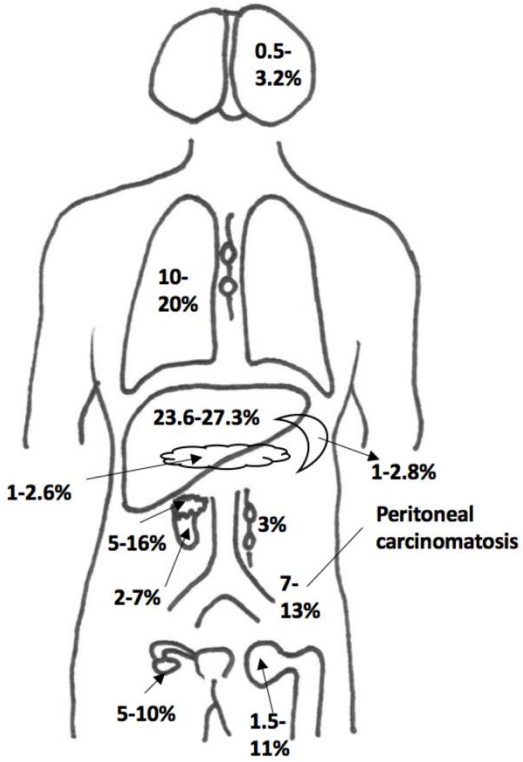


Figure 11. Illustration of reported incidences of distant metastases in colorectal cancer.

1.5 MICROWAVE ABLATION

Thermal ablation is becoming increasingly utilised in the treatment of HCC and metastatic liver tumours. It is used as definitive curative-intended treatment, as a bridge to transplantation in HCC and for debulking of functional neuroendocrine liver metastases for symptomatic relief. A number of ablation modalities have been developed and used, including cryoablation, ethanol ablation and laser ablation, but have been more or less replaced by RFA and MWA. One major drawback with thermal ablation is the high level of local tumour recurrence associated with the procedure. This occurs when the ablation zone does not completely cover the tumour with a sufficient ablation margin. Accurate placement of the antennae and correct estimation of the ablation volume are crucial to optimal outcome of ablation therapy.

1.5.1 Microwave physics and technology

Microwaves are a form of electromagnetic (EM) radiation with frequencies between radio waves and infrared radiation.

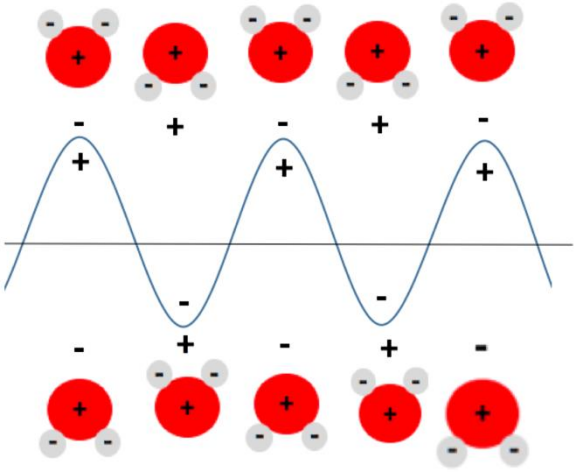


Figure 12. Interaction between water molecules and microwave, displaying water molecule orientation.

EM energy is created in the power generator and distributed through a coaxial cable to the delivering system mostly consisting of an antenna that is placed in the centre of the lesion to be treated. The applied high frequency (915 MHz or 2.45 GHz) EM field alternates polarity billions of times per second and the polar water molecules in the tissue try to continuously realign with the EM field, **Figure 12**. Heat is generated when the molecules fail to keep up with the alternating field and direct heating occurs in a spherical volume around the tip of the antenna that induces coagulative necrosis (199-201). The antenna design is needle-like and the antenna shaft is cooled by circulating saline or water to enable higher power and reduce the risk of skin burns. At the end, the ablation volume is determined by antenna design, tissue type, thermal conduction and heat-sink effect from nearby vessels.

1.5.2 Microwave versus radiofrequency ablation

In a recently published meta-analysis comparing RFA and MWA, one to five-year OS, DFS, local recurrence rate and adverse events were similar (202). Still, MWA offers theoretical advantages over RFA. RFA creates resistive heating when electrical current passes through the ionic tissue medium. It requires an electrical conductivity path and is limited in areas of low electrical conductivity (200). MWA, on the other hand, can heat tissue with high impedance and low electrical or thermal conductivity, such as bone and lung tissue. Microwaves can also penetrate though charred or desiccated tissue (200). The superior thermal properties with faster heating over a larger volume and temperatures of 160-180 °C in contrast to 100 °C with RFA makes the heat-sink effect around larger vessels less (200). Treatment of HCCs less than 5 mm from large vessels has proven safe and with a similar local tumour progression rate and survival as tumours more than 5 mm from larger vessels (203). The above mentioned advantages of MWA over RFA also account for some of its disadvantages, for example injury to adjacent vital structures due to rapid heating (204).

RFA is thought to be more effective in HCC than in liver metastases. Because of cirrhosis and tumour pseudocapsules, the surrounding fibrotic liver of HCC acts as an oven, creating higher temperatures and prolonged cytotoxic temperatures (204). MWA produces more tissue and tumour contraction compared with RFA, something that needs to be accounted for during pre-procedural planning and when assessing treatment response (205).

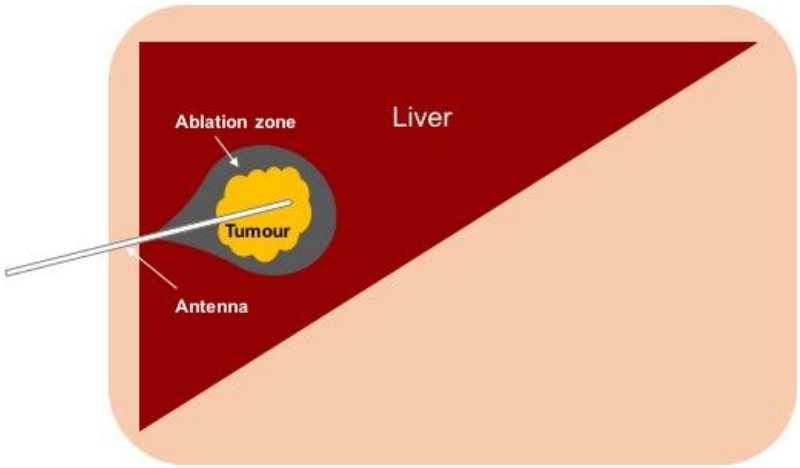


Figure 13. Illustration of percutaneous microwave ablation of a liver tumour.

1.5.3 Microwave ablation – percutaneous, laparoscopic or open approach

MWA can be performed percutaneously **(Figure 13),** laparoscopically **(Figure 14)** or during open surgery **(Figure 15)**. It can be used as a unique intervention modality or synchronous to liver or bowel resection, depending on the clinical situation. Tumour ablation requires real-time visualisation to localize tumours. For tumours not visible on the liver surface, imaging is required for tumour localization and assessment of the spatial relationship to the vascular and biliary structures to ensure accurate guidance and placement of the ablation device. Reports on the initial surgical experience with laparoscopic MWA are emerging, mostly focusing on

the feasibility, safety and technical success, with data on local recurrence rate and long-term survival being sparse (206, 207).

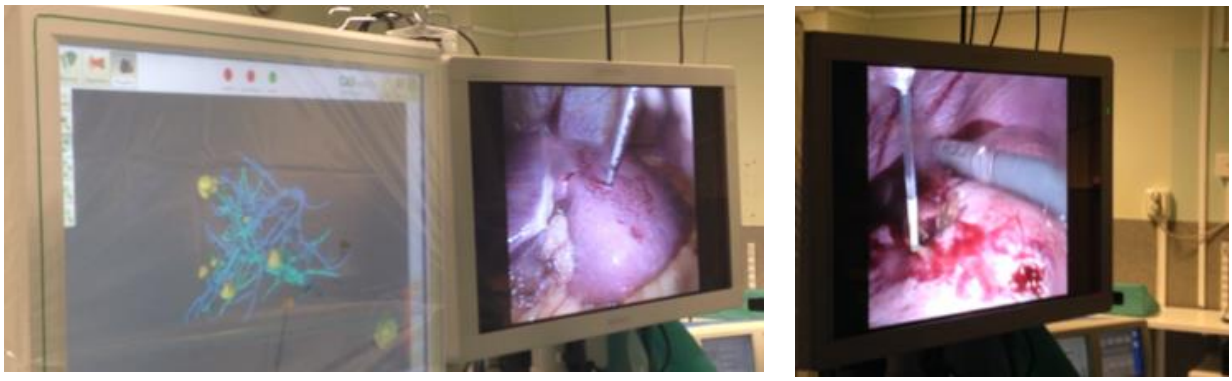


Figure 14. Optical navigated laparoscopic microwave ablation of multiple liver metastases from colorectal cancer, verified with ultrasound assistance, performed at Danderyd Hospital.

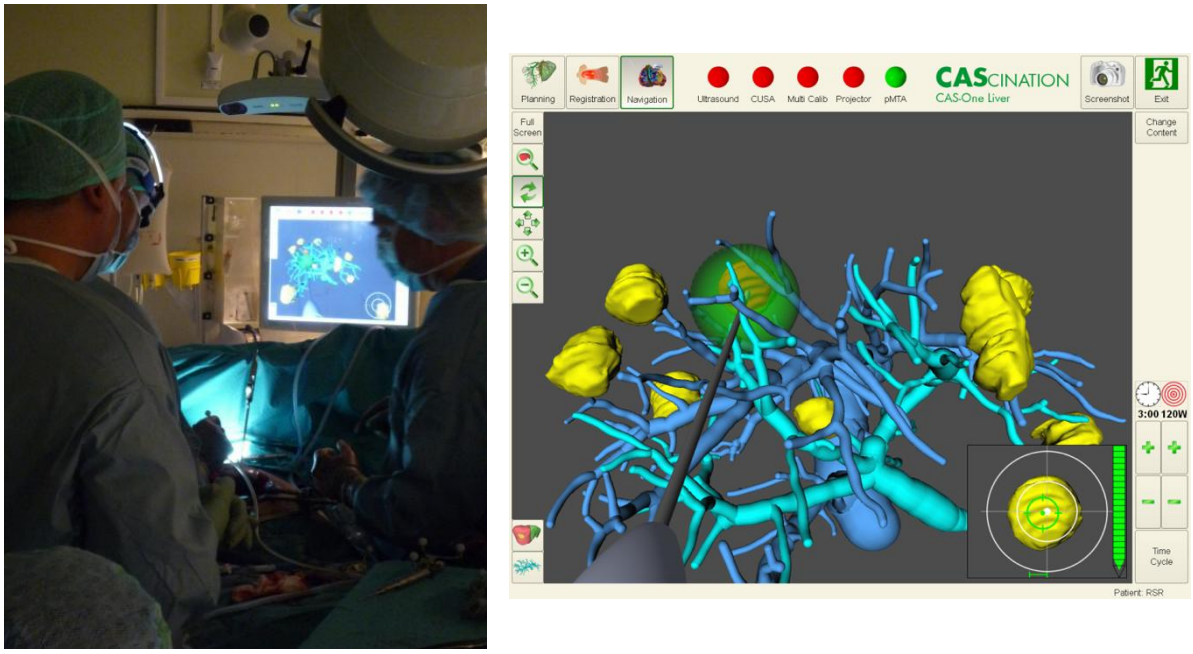


Figure 15. Microwave ablation of 7 colorectal cancer liver metastases during open surgery using an optical tracking system from Cascination AG for tumour guidance.

1.5.4 Image guidance systems

Navigation systems are used by the surgeon or the interventionist to target lesions and for intraoperative orientation. It can be used during percutaneous, laparoscopic (**Figure 14**) and open procedures (**Figure 15**). A reliable and accurate match between the patient's pre-operative imaging and the intraoperative physical space is essential in image-guided surgery. This is particularly challenging in laparoscopic and open surgery when soft tissue deformation occurs. Navigation systems are usually composed of a 3D digitizer interfaced with a computer that displays the actual position of the antenna with respect to cross sectional images of the pre-operative dataset. Accuracy is dependent on how well the antenna is tracked in 3D-space as well as the accuracy and precision of patient-to-image matching.

Tracking systems are based on acoustical, electromechanical, optical or EM systems (208). When using these systems, the navigated antenna still needs to be manually inserted and is hence afflicted by errors due to misinterpretation of displayed navigation data and unintended antenna bending. Free-hand insertion of the antenna is associated with prolonged procedural time and increased lateral error compared with using an aiming device (209).

1.5.4.1 Ultrasound, computed tomography and magnetic resonance imaging navigation

Percutaneous or intraoperative imaging using US is widely used as navigation modality. Intraoperative US has shown to be more sensitive than pre-operative imaging modalities for detecting small lesions (<1 cm). US has the advantage of real-time monitoring of the development of the ablation zone. Major limitations with US include its user dependency, the display of a two-dimensional image in a three-dimensional space and inability to show all lesions (210). CT guidance for percutaneous ablation overcomes many of the drawbacks of US but out-of-plane insertion of antenna is challenging and needs to be interrupted by control scans generating higher doses of irradiation (211). MRI provides even better imaging of soft tissue but requires MR-compatible equipment. Real-time fusion imaging is increasingly used, especially if tumours are not visible by US, and involves overlaying real-time US images onto a previously acquired CT or MRI during the ablation procedure (212).

1.5.4.2 Optical tracking systems

The tracking equipment consists of a minimum of two infrared (IR) position sensor cameras mounted on a trolley-stand, a probe with IR light-emitting diodes and a dynamic reference frame. The IR cameras have a known distance to each other and detect the optical markers, allowing the system to compute the actual coordinates by triangulation in real-time. The dynamic reference frames are attached to the patient and can thereby track the actual position of the patient in space by providing a spatial coordinate system relative to the patients' anatomy. The major limitation of optical IR technology is the requirement of line-of-sight between the dynamic reference frame, the antennae and the cameras (208).

1.5.4.3 Electromagnetic tracking

During EM tracking, a magnetic field is generated and the ablation antenna is equipped with an embedded sensor from where positional information during surgery is provided (208). EM tracking is however sensitive to the presence of metallic objects.

1.5.4.4 Computer-assisted navigation versus robotic systems

Computer-assisted navigation, regardless of whether optical or EM tracking is used, is dependent on the interventionist to execute the antennae insertion in the defined trajectory. Several robotic systems for percutaneous needle-guided interventions using CT or MRI are commercially available and automatically orientate and drive the antenna tip to the intended target position (213, 214). Mean tracking error, defined as the distance between the intended target and the tip of the antennae, of 1.6 to 5.3 mm with robotic guidance systems (215, 216) and 3.6 to 3.8 mm with stereotactic navigation systems are reported (217, 218).

1.5.5 Microwave ablation – outcomes

Clinical studies on outcome after MWA in CRCLM are limited and usually grouped with data on HCC.

1.5.5.1 Technical success and local tumour progression

A multi-centre study of 1007 patients with HCC from China showed a technical success of 97.1% and a local tumour progression (LTP) rate of 5.9% (219). A similar technical success rate of 97.0% was seen in a study from USA involving 450 patients with both HCC and metastases. Local recurrence rate among all patients was 6.0% and highest for HCC (10.1%) and percutaneously treated lesions (14.1%) (220). A review article showed LTP rates of 5.2-24.4% for MWA of HCC and 9.6-14.5% for liver metastases of different origins, using different interventional approaches and treating a wide range of tumour sizes (211). Another review article on ablative therapies for CRCLM, published in 2011, showed a local recurrence rate of 5-13% for MWA and 10-31% for RFA (221). To summarize, local recurrence rates vary substantially between studies with conflicting results as to which degree surgical approach (percutaneously, laparoscopically or open) or tumour type influence results. Most studies, however, report on lower rates of local recurrence in smaller tumours (<3 cm) (222).

1.5.5.2 Complications

Factors that are described to be associated with complications are tumour type, type of approach, number of lesions, tumour location and size, underlying liver disease, the interventionist's experience and associated hepatic resection. Major complications consisting of biliary tract damage, haemorrhage, liver abscess, liver failure, pulmonary complications and perforation of adjacent viscera occur in 3-16% of cases (221). Thermal injuries to adjacent organs can be minimized by different displacement strategies, for example injecting fluid to push the ablation zone away from vulnerable structures (211). The risk for tumour seeding after biopsy or other needle-guided interventions of liver metastases is not negligible, and is estimated to occur in 0.2-4% of cases (223). Three mechanisms are described in which the tumour can seed the needle tract, namely on the needle itself, in bleeding created by the puncture, and from increased intra-tumoural pressure during the intervention (224). Post-ablation syndrome may be the result of an inflammatory response to necrotic tissue and is reported to follow ablation in up to 81% of cases. It occurs from 24 to 48 hours after ablation, lasts up to 10 days, causing fever and flu-like symptoms like malaise, myalgia and nausea. It is usually self-limiting (225).

1.5.5.3 Recurrence free survival and overall survival

Tumour size above 3 cm is predictive of lower recurrence-free survival (220). The one-, three-, and five-year OS in percutaneously treated HCCs were 91.2%, 72.5% and 59.8%, respectively (219). In another review article on MWA of CRCLM, the mean one-, three- and five-year survival was 73%, 30% and 16%, respectively (221).

1.5.5.4 General treatment recommendations for liver metastases

The general cut-off point for thermal ablation is a tumour diameter of 3 cm. However, tumours up to 5 cm are treated with acceptable results (226). Treatment of larger tumours comes at the cost of higher recurrence rate and incomplete ablation.

1.5.6 Ablation versus resection in liver metastases

Most studies demonstrate that resection is superior to RFA and that ablation should only be used in patients unsuitable for resection (227, 228). The question whether RFA could replace resection in certain clinical situations has been investigated in more recent studies. Non-randomized comparisons of resection versus ablation are limited by patient selection, since patients referred for ablation usually have technical contraindications, multiple tumours or comorbidity, potentially reflecting a sub-group with poorer prognosis. In a propensity score analysis, comparing RFA with hepatectomy, RFA was inferior to resection in terms of survival. However, the survival curves were similar for single or small (<2 cm) metastases, raising the question whether ablation might be an option for single, small liver metastases (229). In a study comparing resection with RFA, Park et al. reported results favouring resection with a median survival of 56 versus 36 months for local ablation (230). Similar five-year OS rates of 21% for the RFA group and 23% for the resected group were reported by Reuter et al., with significantly fewer major complications in the ablated group (231).

The local recurrence rate is higher following ablation but the option of a repeat intervention, either surgery or ablation, for recurrent disease still remains and is an important factor to consider in the decision-making process, especially among patients with CRCLM who most likely will present with additional metastases in a near future.

1.6 THERMAL ABLATION OF HEPATOCELLULAR CARCINOMA

HCC is the fifth most common cancer worldwide, the third cause of cancer-related death and accounts for more than 90% of primary liver cancers. Patients with cirrhosis are at risk of developing HCC and surveillance with US is currently recommended in cirrhotic patients who would be treated if diagnosed with the condition. Treatment of HCC is multidisciplinary, including hepatologists, surgeons, medical and radiation oncologists and interventional radiologists. Staging systems in HCC are designed to predict outcome and define treatment assignment. The Barcelona Clinic Liver Cancer (BCLC) classification divides HCC patients into five stages (0, A, B, C and D) based on the extent of disease, Child-Pugh score and Eastern Cooperative Oncology Group performance status, **Figure 16**, (232).

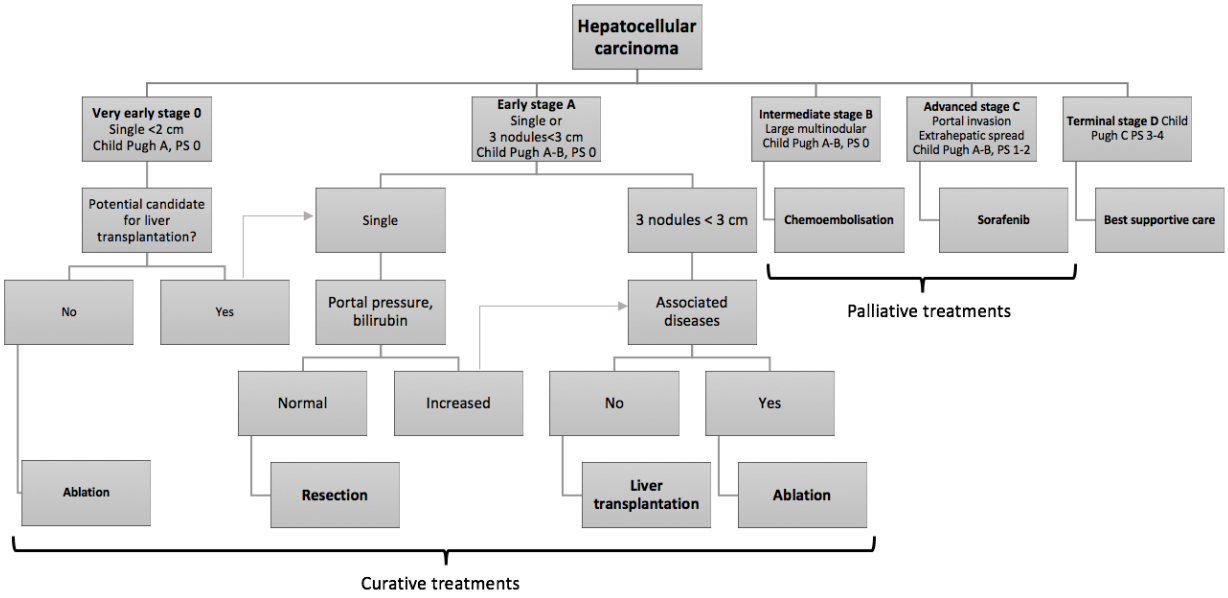


Figure 16. The Barcelona Clinic Liver Cancer staging system and treatment strategy

Surgical resection is the mainstay for treatment of HCC in non-cirrhotic or well-compensated cirrhotic patients and is the first treatment choice in early tumours. In well-selected patients, a five-year survival of 60-80% is achieved (233). Liver transplantation is the first-line treatment in patients with small tumours (<3 nodules <3 cm) or single tumours (<5 cm) and advanced liver dysfunction (Milan criteria) (234). If these criteria are followed, a five-year OS of 50 to 70% is achieved (235).

Local ablation is considered the standard of care for patients with BCLC 0-A tumours not suitable for surgery. RFA is the most widely assessed hyperthermic ablation treatment modality for HCC. Survival after ablation in Child-Pugh A patients is 50-75% at five years, thus paralleling the outcome of surgical resection (232). Observational studies have demonstrated similar survival between surgical resection and thermal ablation in patients with small (<3 cm) HCCs (236, 237). A few randomized controlled trials have compared ablation versus resection, with varying results. Huang et al. found a significantly lower OS in ablated patients compared to resected with a higher recurrence in the RFA group (238), while Chen et al. found no survival differences (239).

2 AIMS

2.1 STUDY I

To provide detailed population-based data on the liver metastatic pattern, treatment and survival in metastatic CRC.

2.2 STUDY II

To evaluate the potentially improved resection rate of CRCLM if all patients with liver metastatic disease were assessed by a liver specific MDT.

2.3 STUDY III

To describe the feasibility and safety of a multiple MWA strategy in patients with initially unresectable CRCLM.

2.4 STUDY IV

The primary aim was to evaluate the accuracy and safety of antenna placement in stereotactic CT-guided MWA of primary and secondary liver tumours. Secondary aims were to evaluate the feasibility and radiation dose associated with the navigation system and to assess the safety of high-frequency jet ventilation for target motion control.

3 PATIENTS AND METHODS

3.1 STUDY I

3.1.1.1 Study population

All patients diagnosed with CRC in the counties of Stockholm and Gotland from the 1st of January 2008 to the 31th of December 2008, treated at nine different hospitals, were identified from the Swedish Colorectal Cancer Registry (SCCR).

3.1.1.2 Methods – data collection

Data on TNM stage, date and type of surgery were retrieved from the registry. All Swedish citizens are assigned a unique personal identification number at birth, which is also registered in the SCCR and was used to identify each patient in the different hospital electronic patient records. All clinical records were reviewed from date of diagnosis of CRC and at least five years afterwards, or until death. Date of diagnosis of metastatic disease was registered and detailed information on liver and lung metastases (number and segmental distribution) and the location of all other extrahepatic metastases were collected. Referral to a colorectal MDT and liver MDT were documented. Treatment for primary tumour and treatment of metastases, oncologic and surgical, were recorded. Synchronous liver metastases were defined as metastases detected prior to or during resection of the primary tumour, and in non-resected patients, as prior to or at the same time as the diagnosis of the primary tumour. Primary tumour location was retrieved from the electronic patient record. Midgut tumours were defined as tumours originating from the cecum, ascending colon and transverse colon while hindgut tumours were defined as tumours originating from the splenic flexure and distally.

3.2 STUDY II

3.2.1.1 Study population

All patients from study I, identified with synchronous or metachronous liver metastases, irrespective of extrahepatic disease, detected during a five-year follow-up period, constituted the study cohort of study II.

3.2.1.2 Methods – data collection

Additional information on each patient was retrieved from the electronic patient records. Comorbidity according to the ASA grade, WHO performance status and relevant blood results (albumin, creatinine, liver enzymes and bilirubin) were documented. The discussion and decision made at a previous colorectal MDT and/or liver specific MDT was documented, as was the patient's own preference towards treatment. Decisions made by a MDT regarding resectability of liver metastases were noted and patients were classified as resectable, potentially resectable or unresectable.

3.2.1.3 Evaluation of imaging studies

All available thoraco-abdominal imaging studies were reviewed by a hepato-pancreato-biliary-radiologist, assessing the location, number and size of intra- and extrahepatic metastases as well as local recurrence at the primary tumour site. For each patient, the imaging was classified according to a radiological classification system that was created for the purpose of the study, **Table 6**.

Table 6. Radiology classification system designed to evaluate imaging for study II.

Grade	Description
5	State-of-the-art (MRI with liver-specific contrast and DW imaging)
4	Diagnostic, good technique
3	Diagnostic, poor technique
2	Non-diagnostic, good technique
1	Non-diagnostic, poor technique

Diffusion-weighted (DW). The term "diagnostic" refers to whether the imaging was sufficient to make a complete assessment and treatment planning. For example, a CT examination without intravenous contrast in a patient with innumerable metastases in all liver segments, is a "poor" technique but still diagnostic for the purpose of the study.

3.2.1.4 Creation of a fictive multidisciplinary team conference

A fictive liver MDT conference was composed, consisting of four liver surgeons, three medical oncologists, one diagnostic radiologist and one presenting physician. Each patient was presented for the audience, as he or she would have been at an actual liver MDT, including age, gender, medical history, existing extrahepatic disease, whether or not the primary tumour was resected/deemed resectable by a colorectal surgeon and if known, the patient's own preference towards treatment of liver metastases. The radiologist demonstrated all available images and the conference participants decided on a treatment strategy for each patient based on the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Metastatic colorectal cancer, published in 2014, dividing patients into three groups: resectable, potentially resectable and unlikely/never resectable (87).

3.3 STUDY III

3.3.1.1 Study populations

Twenty patients with primarily unresectable liver metastases, all discussed at the regional liver MDT conference, who could not be rendered tumour-free because of the absence of a tumour-free FLR due to the extent of segmental involvement were treated with a multiple MWA strategy, with or without local resection. The outcome of the ablated group was compared with two historic cohorts selected from the study population of study I. The first cohort consisted of all resected patients with metastases smaller than 30 mm. The second cohort consisted of all patients who had been treated with palliative chemotherapy for their liver metastatic disease, were <85 years old, had <20 metastases smaller than 30 mm and no unresectable extrahepatic disease and, hence, theoretically, could have been treated with

thermal ablation therapy. These two groups represented the best-case and worse-case scenarios.

3.3.1.2 Methods

All interventions were done with curative intent and a prerequisite was that the whole liver could be rendered macroscopically tumour-free. MWA (Acculis MTA, Angiodynamics, Latham, NY, USA) of lesions <35 mm was performed at laparotomy with intraoperative US guidance (n=13) or computer-assisted navigation (n=7) (CASOne, Cascination AG, Bern, Switzerland) (240). Lesions engaging the liver surface were resected in some patients.

3.4 STUDY IV

3.4.1.1 Study population

Twenty patients with primary or secondary liver tumours, evaluated at the regional liver MDT conference and assessed to have unresectable tumours or not fit for resection and fulfilling the inclusion/exclusion criteria, **Table 7**, were asked to participate in the study and signed the consent form after reading study information (**Appendix A**). Child Pugh Score and interpretation are outlined in **Table 8**.

Table 7. Inclusion and exclusion criteria for study IV.

Inclusion criteria	Exclusion criteria
Liver tumours not visible on US or not accessible by percutaneous US-guidance	Non-correctable coagulation disorder or Child-Pugh Score C
Male patients > 18 years Non-pregnant, non-lactating females age >18 years	Renal insufficiency (Creatinine>250) Condition requiring haemodialysis
Written informed consent	A mental condition rendering the patient unable to provide informed consent
Tumours <30 mm, 1-2 tumours[a]	

[a] Progression of target tumour or additional tumours beyond the tumour-related inclusion criteria detected on the day of intervention were not regarded as reasons for exclusion.

Tale 8. Child-Pugh Classification and interpretation.

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L	<34	34-50	>50
Serum albumin, g/L	>35	28-35	<28
PK (INR[a])	<1.7	1.7-2.3	>2.3
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV
Points	**Class**	**One-year survival**	**Two-year survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

[a] International normalized ratio (INR).

3.4.1.2 Methods - navigation system, aiming device and microwave ablation system

A navigation system (CAS-One IR, Cascination AG, Switzerland) (**Figure 17, 1**) dedicated to stereotactic computer-assisted procedures was used. The main components of the system are the optical position measurement system (NDI Vicra, Northern Digital, Canada) (**Figure 17, 2**), a set of retro-reflective, self-adhesive single skin markers (**Figure 17, 3**) and a 4-degree of freedom aiming device (**Figure 17, 4**) attached to a 7-degree of freedom holding arm (iSYS, Medizintechnik, GmbH, Austria) (**Figure 17, 5**). Detailed information on the function of the aiming device and the advantage compared to free-hand navigation has been described by Wallach et al. (209). MWA was performed with a 1.8 mm water-cooled antenna with the use of a 2.45 GHz generator (Accu2i, Microsulis Medical) (**Figure 17, 6**).

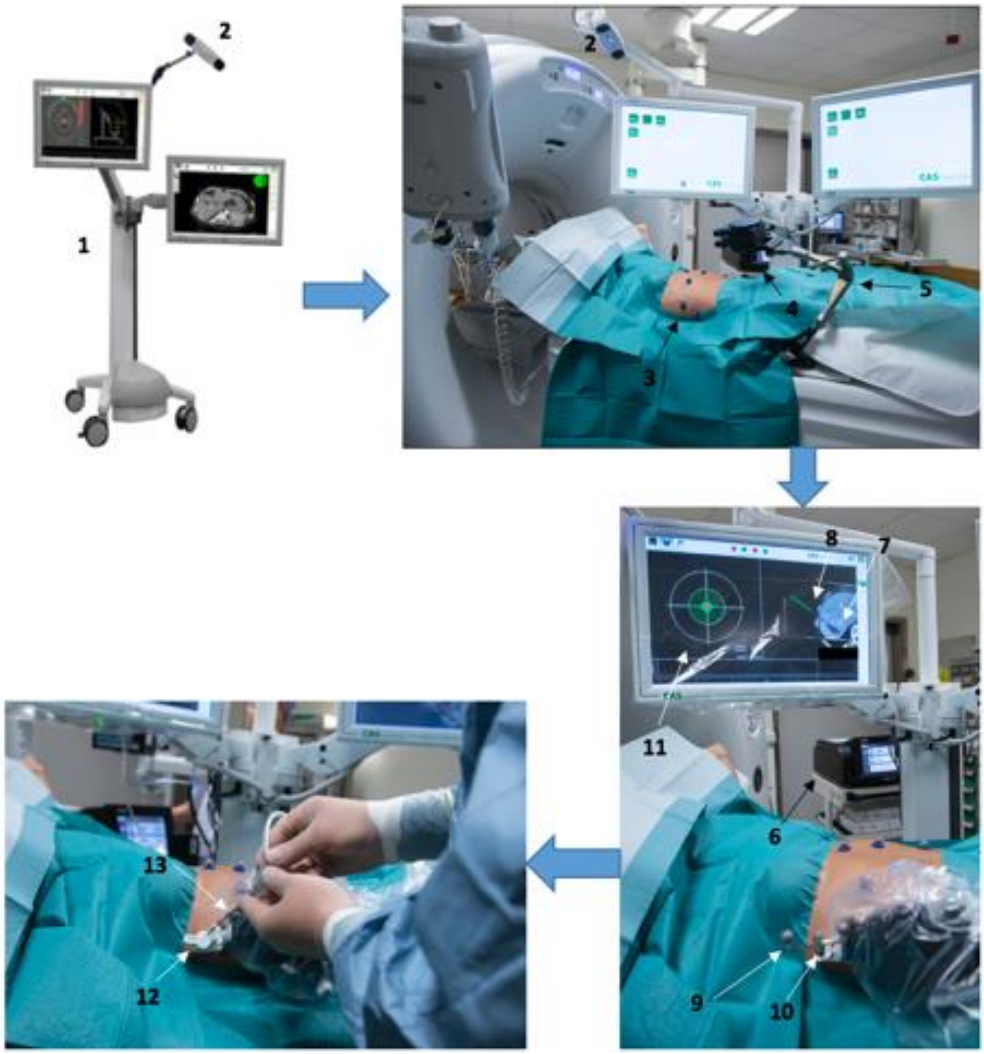


Figure 17. Flow-chart illustrating the procedure of study IV with detailed explanation in the text.

3.4.1.3 Patient set-up

The patients were placed on the CT table in a supine position. General anaesthesia with intermittent intravenous neuromuscular block allowed immobilization. High-frequency jet ventilation (HFJV) (Monsoon III ventilator, Acutronic Medical Systems AG, Hirzel, Switzerland) was used to minimize ventilation-induced liver movement. HFJV is a method for mechanical ventilation where short-duration pulses of pressurized gas are delivered in a

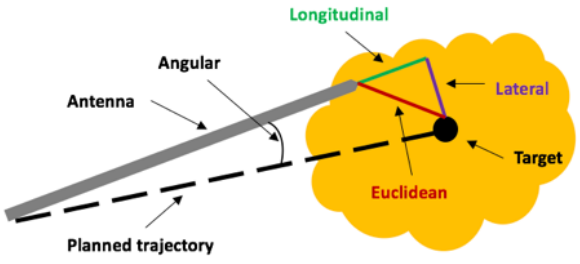
high-flow manner through a small catheter in the trachea (241). Adequate intraoperative monitoring and expiratory CO_2 measurements were performed to enable adjustments of HFJV settings and avoid hypercapnia.

3.4.1.4 Procedure

Self-adhesive reflective single markers were glued onto the patient's skin, enabling both automatic image-to-patient registration and continuous tracking of patient surface deformation and movement (**Figure 17, 3**). CT images with complete liver coverage were acquired during HFJV and transferred to the navigation system (**Figure 17, 1**). On the navigation system, target locations (**Figure 17, 7**) as well as the most appropriate antenna trajectory (**Figure 17, 8**), avoiding ribs, lungs and major bile ducts and vessels were identified manually and displayed in a 3D off-plane reconstruction. A pre-calibrated dynamic reference base (**Figure 17, 9**) was placed in the antenna guide adapter (**Figure 17, 10**) and roughly positioned along the planned antenna insertion point, with the help of a 3D reconstruction of the skin surface presented on the screen and a 2D targeting viewer (**Figure 17, 11**) for fine alignment. The dynamic reference base was then replaced by an antenna guide (**Figure 17, 12**) through which the MW-antenna (**Figure 17, 13**) was inserted to the planned depth with the active point of the antenna in the centre of the lesion. A control CT was performed and if the antenna was assessed as accurately placed, MWA was conducted, and if located non-optimally, the antenna was repositioned. Ablation time and energy was calculated based on tumour size and proximity to vascular and biliary structures, according to the manufacturer's guidelines and operator discretion.

3.4.1.5 Post-procedural follow-up

After the intervention, the patient was transferred to the post-operative ward and discharged the same or following day. A control CT was performed at day 5-10, to evaluate the ablation zone, and then repeatedly according to local follow-up guidelines with MRI or CT depending on the type of malignancy. Perioperative morbidity was assessed 30 days post-ablation when a follow-up visit was scheduled.



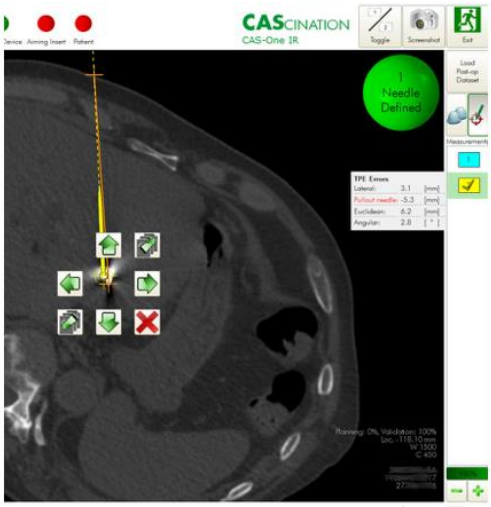


Figure 18 (right). Intraoperative validation module. Yellow hair-cross is the target and orange hair-cross corresponds to the actual antenna tip. **Figure 19 (above left).** Illustration of different components in target positioning error.

3.4.1.6 Data analysis

Antenna insertion accuracy was evaluated retrospectively with an intraoperative validation module integrated into the navigation system, **Figure 18**. The intraoperative validation module fuses post-insertion control CT with pre-insertion navigation/planning CT and compares the planned trajectory with the achieved antenna position and calculates the target positioning error (TPE) – the euclidean distance between the actual antenna tip position measured on the control CT and the desired antenna position defined pre-operatively on the navigation CT, **Figure 19**. Additional study endpoints are outlined in **Table 9**.

Table 9. Explanation of additional study endpoints

Parameter	Description
Tumour size	Maximum tumour diameter
Tumour location depth	Distance between antenna's skin-entry point and the intended target
Cranio-caudal orientation angle	Antenna trajectory orientation angle on the sagittal plane defined by y-z axis of the patient coordinate system
Orbital orientation angle	Antenna trajectory orientation angle on the axial plane defined by x-y axis of the patient coordinate system
Procedure time	Duration from the acquisition of the first planning scan to the withdrawal of the antenna; including planning, preparation time, aiming device alignment, needle insertion, and ablation time (minutes)
Number of complications	Number of intervention-related complications, according to standardized SIR classification system (242)
Patient radiation exposure	Radiation exposure expressed as dose-length product (DLP)
Lateral error	A normal distance between the planned trajectory and the antenna at the planned target position
Depth error	A longitudinal distance from the antenna tip to the target along the planned trajectory
Total error	Euclidean distance between the achieved antenna tip position and the planned target position
Angular error	A deviation between the planned trajectory axis and the achieved antenna axis
Number of antenna readjustments	Number of times the needle was repositioned to better target the intended target area
Dose-length product (DLP)	$CTDI_{vol}$ (a measure of exposure per slice) x irradiated length. DLP_{total} = total radiation dose. DLP_{inter} = an interventional dose corresponds to the radiation introduced by antenna verification scans

3.5 STATISTICS

For studies I, II, III and IV, p-values < 0.05 were considered statistically significant. Kaplan-Meier plots were used to display survival probabilities and log-rank test for testing equality of survival functions between groups in studies I, II and III. For studies I and II, statistical analyses were performed using STATA 13 and for studies III and IV, STATA 10 was used (StataCorp, College Station, Texas 77845 USA).

3.5.1.1 Study I

Categorical data were presented as frequencies/proportions and analysed with Pearson's chi-square test. Continuous variables (age) were described as medians and analysed with the Wilcoxon rank-sum test (non-normally distributed data). Logistic regression was used to calculate unadjusted and adjusted odds ratios (ORs) for factors associated with the probability of undergoing a liver intervention, controlling for possible confounders hypothesized as being age (dichotomized into ≤ or >68 [median]), sex, tumour stage (dichotomized as T1/T2 and T3/T4), nodal status (dichotomized as N0 and N1/N2), synchronous/metachronous and number of liver metastases (categorized into 1-2, 3-4 and ≥5 lesions). Variables with $p<0.10$ in the univariable analyses were included in the multivariable analysis and presented with a 95% confidence interval (CI). The Cox proportional hazards model was used to identify risk factors affecting survival, calculating hazard ratios with 95% CI. Potential risk factors included in the model were age (continuous variable), sex, tumour and nodal stage (dichotomized as described above), primary tumour origin (midgut/hindgut), presence of liver metastases, lung metastases and extrahepatic disease. In patients with liver metastases, included risk factors were age, sex, tumour and nodal stage (as above), primary tumour origin (midgut/hindgut), synchronous versus metachronous detection, size of liver metastases (dichotomized into ≤50 mm and >50 mm), number of liver metastases (categorized as above), liver resection and the presence of lung metastases.

3.5.1.2 Study II

Baseline characteristics were assessed and tested as described for study I. Logistic regression was used to calculate ORs for factors predictive of referral to the liver MDT conference, adjusting for age (dichotomized into ≤ or >68 [median]), sex, ASA grade, treatment at a teaching hospital, synchronous/metachronous and number of liver metastases (categorized into 1-5, 6-10 and >10 liver metastases). Variables with $p<0.15$ in the univariable analysis were included in the multivariable model. Cohen's Kappa for interrater agreement was used to determine the overall agreement between the original and fictive liver MDT conference, analysing resectable/potentially resectable versus unresectable, and $\kappa>0.7$ was considered acceptable.

3.5.1.3 Study III

Baseline characteristics were defined and analysed as described for study I with the addition of Fisher's exact test for proportions. Cox proportional hazards model was used to identify

independent predictors of survival. The two predictors with the lowest p-values were kept in the multivariable analysis.

3.5.1.4 Study IV

Patient and tumour characteristics and target errors were presented with mean (±SD), frequencies (percentage) and median (min-max). Correlation between tumour location depth and targeting accuracy was tested with the nonparametric Spearman rank correlation test. A power calculation was performed based on previous experiments on cadavers where a TPE of 3.1 ± 1.2 mm was achieved. An inferior TPE of 4.0 ± 1.2 was expected in humans. The power calculation revealed that a sample size of 16 was required to achieve a power of 0.8 at a significance level of 0.05. The study was oversampled by four patients to cover for potential loss.

3.6 ETHICS

The regional ethical review board at Karolinska Institutet, Stockholm, approved studies I, II, III and IV. The local radiation protection committee at Danderyd hospital approved of study IV.

4 RESULTS

4.1 STUDY I

During 2008, a total of 1026 patients were diagnosed with CRC of whom 52.7% were male and 47.3% female with males being significantly younger than females (p<0.001).

4.1.1.1 Liver metastatic patterns

During a median follow-up of 63 months, liver metastases were detected in 272 (26.5%) patients and more often in males than females (29.0% versus 23.7%, p=0.054) with no observed age difference (p=0.397). The demographic and clinico-pathological features of patients with and without liver metastases are outlined in **Table 10**. Patients with hindgut cancer were significantly more often diagnosed with liver metastases than patients with midgut cancer (28.4% versus 22.1%, p=0.029). However, patients with liver metastatic midgut cancer had a higher tumour burden in terms of number of liver metastases and extent of segmental involvement.

Patients with synchronously detected liver metastases (16.2%) had a higher tumour burden than patients with metachronous detected metastases (10.3%) (>4 metastases: 67.5% versus 34.0%, p<0.001 and 7 to 8 segments: 39.8% versus 13.2%, p<0.001). Synchronous versus metachronous detection of liver metastases was not influenced by age (p=0.950), sex (p=0.478) or embryologic (p=0.096) or anatomical origin (p=0.127) of the primary cancer. Seventy-six percent of all detected liver metastases were diagnosed within one year, 89% within two years and 93% within three years of diagnosis of primary tumour. At detection of liver metastases, 81 patients (48.8% of those with synchronous liver metastases) had liver-only metastases and 60 patients had widespread metastases engaging all liver segments. One hundred and three patients (37.9%) had liver-only metastases and no further extrahepatic metastases detected during the follow-up period.

4.1.1.2 Extrahepatic metastases

Extrahepatic metastases were diagnosed in 251 patients (24.5%). The most common extrahepatic site was the lungs (174 patients, 16.9%), followed by peritoneal carcinomatosis (73 patients, 7.1%) and distant lymph nodes (49 patients, 4.8%). Lung metastases were significantly more often diagnosed in patients with metachronously detected liver metastases (56.6% versus 44.0%, p=0.042). Fifty-one percent of lung metastases were diagnosed within one year, 75% within two years and 84% within three years from diagnosis of the primary tumour. Patients with hindgut cancer were more often diagnosed with lung metastases (19.7% versus 13.2%, p=0.010) and peritoneal carcinomatosis was more frequent in midgut cancer (10.6% versus 5.5%, p=0.003).

Table 10. Demographic and clinic-pathological features of patients with and without liver metastases

	All patients (n=1026)		No liver metastases (n=754)	Liver metastases (n=272)	p[a]
Age (years)[c]	71.0 (62.2-79.9)		71.9 (63.5-81.0)	68.0 (60.1-77.4)	<0.001[b]
Male	69.8 (62.1-77.5)		70.5 (62.3-78.1)	67.5 (60.3-75.1)	0.021[b]
Female	72.6 (63.3-83.2)		74.2 (65.4-84.1)	68.9 (59.4-79.9)	0.001[b]
Age category					
<50	55 (5.4)		35 (4.6)	20 (7.4)	0.001
51-65	306 (29.8)		206 (27.3)	100 (36.8)	
66-80	413 (40.3)		309 (41.0)	104 (38.2)	
>80	252 (24.5)		204 (27.1)	48 (17.6)	
Sex ratio (M : F)	541 : 485		384:370	157 : 115	0.054
Primary tumour position [d]					
Midgut tumours	349 (34.9)		272 (36.9)	77 (29.4)	0.029
Hindgut tumours	651 (65.1)		466 (63.1)	185 (70.6)	
Tumour category [e]					
T0	12 (1.2)		11 (1.5)	1 (0.4)	
T1	90 (8.8)		85 (11.3)	5 (1.8)	<0.001
T2	145 (14.1)		138 (18.3)	7 (2.6)	
T3	520 (50.7)		389 (51.6)	131 (48.2)	
T4	201 (19.6)		105 (13.9)	96 (35.3)	
Unknown	58 (5.6)		26 (3.4)	32 (11.7)	
Node category [e]					
N0	513 (50.0)		470 (62.3)	43 (15.8)	<0.001
N1	333 (32.5)		192 (25.5)	141 (51.8)	
N2	82 (8.0)		45 (6.0)	37 (13.6)	
Unknown	98 (9.5)		47 (6.2)	51 (18.8)	
Metastatic category [e]				<0.001	
M0	773 (75.4)		689 (91.4)	84 (30.9)	<0.001
M1	224 (21.8)		37 (4.9)	187 (68.8)	
Unknown	29 (2.8)		28 (3.7)	1 (0.3)	
TNM-stage [e]					
Stage I	194 (18.9)		191 (25.3)	3 (1.1)	<0.001
Stage II	299 (29.1)		274 (36.4)	25 (9.1)	
Stage III	267 (26.0)		213 (28.2)	54 (19.9)	
Stage IV	224 (21.8)		37 (4.9)	187 (68.8)	
Unknown	42 (0.4)		39 (5.2)	3 (1.1)	

Values in parentheses are percentages unless indicated otherwise. [a]Chi2 test, except [b]Wilcoxon rank-sum test. [c]Values are median (i.q.r). [d]According to embryologic origin excluding unknown primaries (n=11) and multiple primaries (n=15). [e]Stage at initial diagnosis.

4.1.1.3 Treatment of liver and extrahepatic metastases

Of all patients with liver metastases, 102 (37.5%) were referred to the liver multidisciplinary team conference and 69 (25.4%) were treated with resection, ablation or a combination of the two methods, with a recurrence rate of 42%. Of the 251 patients where extrahepatic metastases were detected, 30 (12%) were resected/ablated with curative intent. The probability of undergoing a liver resection was associated with age ≤68 years (OR 2.79, CI 1.37-5.69), T-stage (T3-T4 versus T1-T2, OR 0.15, CI 0.03-0.77) and number of liver metastases (>5 versus 1-2, OR 0.07, CI 0.02-0.18) while in the multivariable analysis sex, metachronous presentation and nodal stage was not.

4.1.1.4 Survival

Five-year OS in the entire cohort was 56.2% (median survival not reached). Patients with liver metastases had a significantly lower five-year OS compared to patients without liver metastases (16.9% versus 70.4%, p=0.001).

Factors identified as poor predictors of survival in the multivariable analysis among patients with CRC were increasing age (HR 1.04, CI 1.03-1.05), higher T-stage (T3-T4 versus T1-T2, HR 1.40, CI 1.01-1.93) and higher N-stage (N1-N2 versus N0, HR 1.62, CI 1.29-2.04), as well as the presence of liver metastases (HR 3.38, CI 2.57-4.44) and extrahepatic metastases (non-lung metastases, HR 2.05, CI 1.56-2.69). Sex (HR 1.09, CI 0.91-1.30), the presence of lung metastases (HR 1.23, CI 0.93-1.62) and primary tumour location (HR 0.90, CI 0.74-1.09) were not significantly associated with survival. In the multivariable analysis of patients *with* liver metastases, higher age (HR 1.03, CI 1.01-1.05), hindgut tumour origin (HR 0.56, CI 0.39-0.79), size of liver metastases > 50 mm (HR 2.51, CI 1.73-3.65) and liver resection (HR 0.21, CI 0.13-0.33) remained significant predictors of survival. Also in this setting, the presence of lung metastases (HR 1.11, CI 0.80-1.53) and sex (HR 0.91, CI 0.65-1.28) did not influence OS.

In patients with liver metastases, midgut cancers had a significantly worse OS compared to hindgut cancers with a two-year survival of 22.1% and 51.9%, respectively, and a five-year survival of 6.5% and 21.6%, respectively (p<0.001), irrespective of treatment strategy, **Figure 20**.

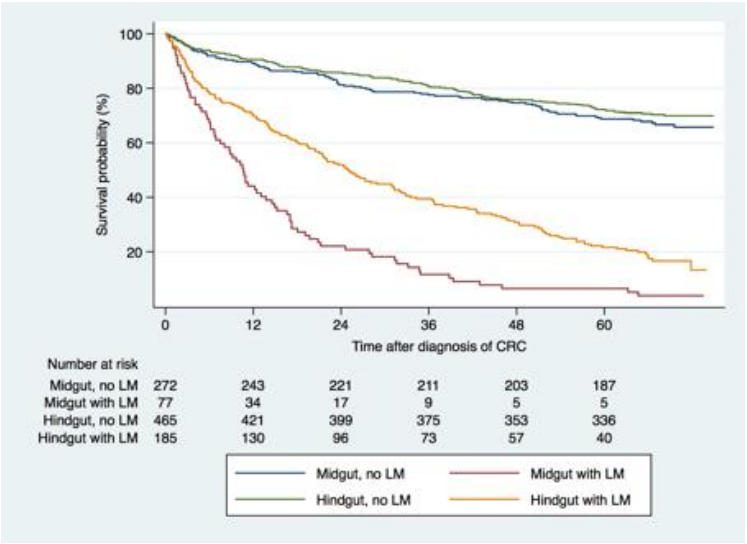


Figure 20. Kaplan-Meier curves showing overall survival in patients with midgut and hindgut tumours with or without liver metastases (LM).

The same survival pattern was seen in patients with lung metastases with a five-year survival of 13.0% versus 21.9% (midgut versus hindgut origin, p=0.008).

The one- and five-year survival rates of patients with liver metastases treated with resection, palliative chemotherapy or best supportive care were 92.8% and 48.6%, 58.1% and 2.2%, and 8.2% and 0.0% respectively, counting from the date of diagnosis of liver metastases, **Figure 21**.

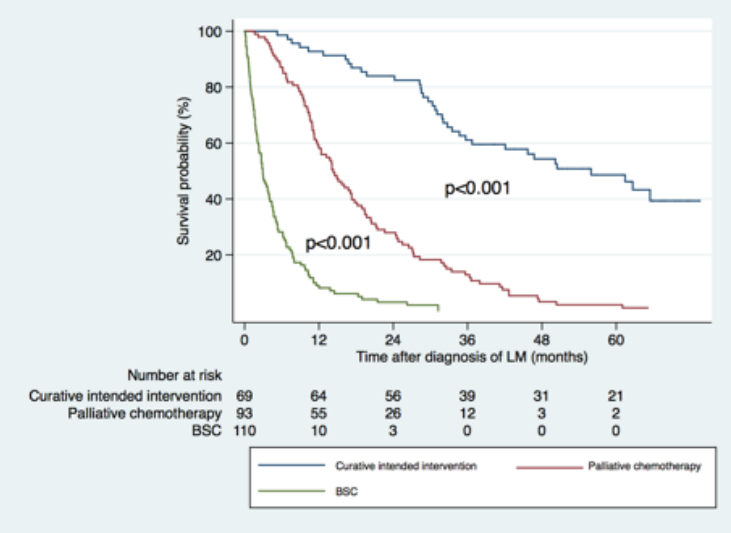


Figure 21. Kaplan-Meier curves showing overall survival in patients with liver metastases treated with curative-intended intervention, palliative chemotherapy or best supportive care (BSC).

In **Figure 22**, survival of patients with non-metastatic CRC is compared to patients with different metastatic patterns in terms of liver and lung metastases. Patients without metastatic disease had a five-year survival of 75% compared with 45.7%, 25.2% and 12.7%, respectively, for patients with lung metastases only, liver metastases only, and liver and lung metastases combined (corresponding to a median survival of 4.3, 1.4 and 1.8 years, respectively).

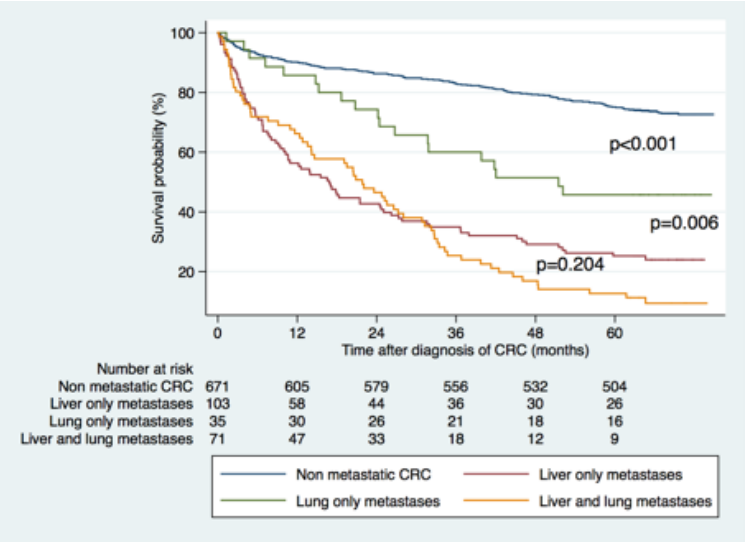


Figure 22. Kaplan-Meier curves showing overall survival in patients with non-metastatic colorectal cancer and different metastatic pattern.

4.2 STUDY II

4.2.1.1 Results from the original liver multidisciplinary team conference

Of 1026 patients diagnosed with CRC during 2008, 272 developed liver metastases of which 235 patients were evaluated at a colorectal MDT and 102 were further referred and discussed at a liver MDT conference, **Figure 23**. Out of the 133 patients not referred to the liver MDT, 55 were considered by the local colorectal team as to have unresectable liver metastases, 26 as having unresectable extrahepatic disease, 42 as having a combination of both unresectable liver and extrahepatic disease and the remaining were not referred for a variety of other reasons. Thirty-seven were not evaluated in a MDT setting at all.

Factors associated with the referral to a liver MDT were age (OR 3.12, CI 1.72-5.65), ASA score (ASA 2 versus 3, OR 0.34, CI 0.18-0.63) and number of liver metastases (1-5 versus 6-10 and >10, OR 0.16 (CI 0.06-0.41) and OR 0.10 (CI 0.04-0.22), respectively). Sex, treatment at a teaching hospital, and metachronous detection did not influence the referral rate.

Referral rate to the liver MDT ranged from 0% to 48.6% between the different hospitals of the region. When excluding two hospitals which treated less than 10 patients with liver metastases, the referral rate ranged between 28.6% and 48.6% (p=0.505).

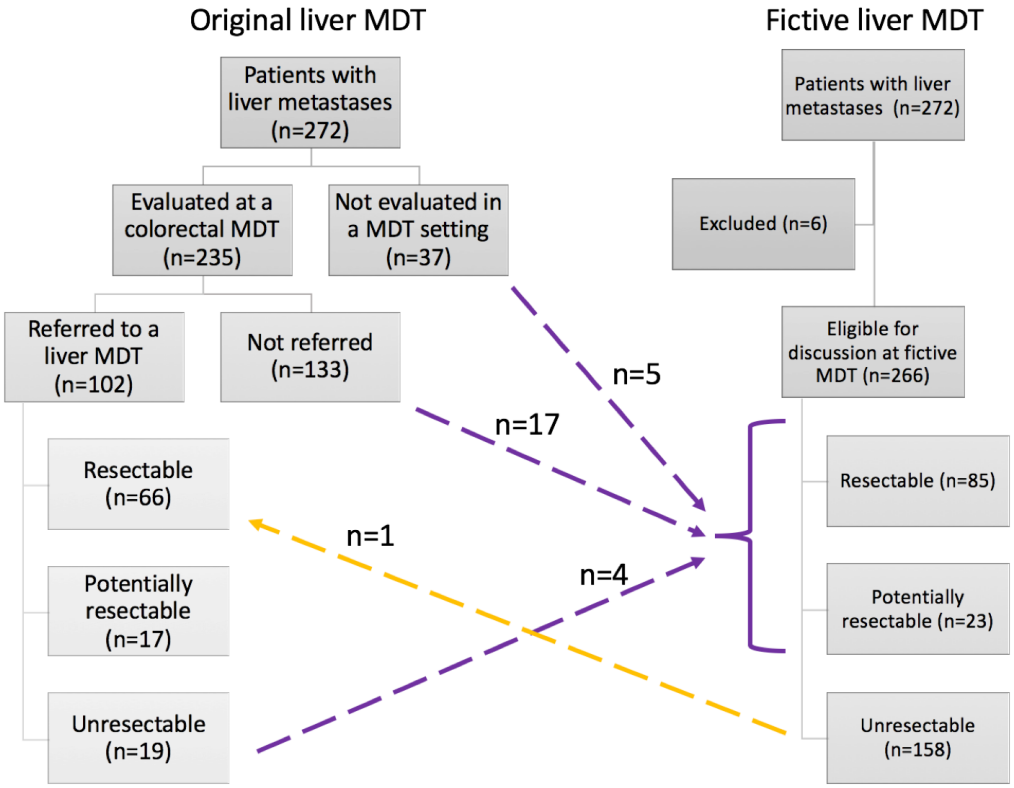


Figure 23. Flow-chart illustrating the decisions made at the original liver MDT and at the fictive liver MDT

4.2.1.2 Results from the fictive liver MDT conference

Imaging for re-evaluation could not be retrieved for six patients who were then excluded from the analysis. Results from the fictive liver MDT are shown in **Figure 23**. Twenty-two out of 170 patients originally not managed by a hepatobiliary surgeon, were assessed as resectable/potentially resectable at the fictive liver MDT. These 22 patients as a group had a higher median age (p=0.005), a higher proportion of emergency surgery of the primary tumour (p=0.002) and higher proportion of patients with more than 5 liver metastases compared with the patients that were actually referred to the liver MDT. However, ASA score (p=0.523) and synchronous detection (p=0.361) did not differ. Median OS among the 22 patients was 12 months compared with 55.9 months for patients originally discussed at a liver MDT and resected and 19.4 months for patients originally discussed at a liver MDT and not resected.

Primary reasons for unresectability (n=158), as assessed at the fictive liver MDT were extrahepatic disease (n=40), extent of liver metastases (n=39), a combination of extensive liver and extrahepatic disease (n=34), unresectable CRC or unresectable local recurrence (n=20), comorbidity (n=12), age (n=8) and patient preference (n=5).

Actual treatment decisions among those with resectable or potentially resectable liver metastases made at the original liver MDT and during the fictive liver MDT were the same in 95.1% of patients (Cohens's Kappa 0.83). The original and fictive liver MDT conferences disagreed on the management of five patients **(Figure 23)**. One patient, assessed as potentially resectable with local ablation at the original liver MDT conference were not assessed as even potentially resectable at the fictive liver MDT. On the contrary, four patients were evaluated as potentially resectable at the fictive liver MDT, but not at the original liver MDT conference. The motivations for the decisions at the original MDT were bilateral disease, a too small FLR, one complicated located LM and the last patient as unresectable because of extrahepatic disease (a single lung metastasis and a single metastasis of the abdominal wall).

The quality of liver imaging is outlined in **Table 11**.

Table 11. Classification of imaging in 266 patients with liver metastases

Grade	Description	Distribution in study population n (%)
5	State-of-the-art (MRI with liver-specific contrast and DW imaging)	3 (1.1)
4	Diagnostic, good technique	189 (71.1)
3	Diagnostic, poor technique	27 (10.1)
2	Non-diagnostic, good technique	45 (16.9)
1	Non-diagnostic, poor technique	2 (0.8)

Numbers in parenthesis are percentage. Magnetic resonance imaging (MRI). Diffusion-weighted imaging (DW)

4.3 STUDY III

4.3.1.1 Patients' treatment outcome

Twenty patients with multiple CRCLM were treated with the multiple MWA strategy between October 2009 and September 2012. The control groups consisted of 25 palliatively treated and 36 resected patients selected from the 272 patients with liver metastases in the five-year follow-up of 1026 patients presenting with CRC during 2008 from study I. Patient and tumour characteristics are presented in **Table 12** and treatment-related parameters in the multiple MWA strategy-group in **Table 13**. Simultaneous local resection of metastases was performed in four patients. In one patient, the strategy was changed intraoperatively from the MWA strategy to a two-stage procedure with initial clearance of the left liver followed by a right hemihepatectomy at a later stage. Major complications (Clavien-Dindo classification 3-4) occurred in five patients. One patient suffered from multiple liver abscesses and another developed a pleural effusion, both of which were treated with percutaneous drainage. Three patients had respiratory failure treated with non-invasive ventilation support.

Table 12. Patient and tumour characteristics

	MWA n=20	**Resected n=36**	**Palliative n=25**	**P[b]**
Age (years), median (min-max)	64 (44-82)	65 (42-83)	68 (49-83)	0.75
Male : female	9 : 11	23 : 13	15 : 10	0.38
Synchronous/ metachronous	18 : 2	17 : 19	15 : 10	<0.05
Number, median (min-max)	9 (5-22)	2 (1-15)	5 (1-16)	<0.05
Size (mm)[a], median (min-max)	27 (10-54)	17 (6-30)	19 (10-28)	0.07

[a]Size at initial presentation. [b]MWA group versus palliative group.

Table 13. Treatment-related parameters in the MWA group

Number of ablations	7 (4-22)
Procedure time (min)	235 (112-475)
Length of hospital stay (days)	10 (2-24)
Relation of ablation to colorectal surgery	Numbers
Before	3
Simultaneously	12
After	5
Navigation	
Ultrasound	13
Computer-assisted	7
Complications[a]	
Minor (Grade 1-2)	7
Major (Grade 3-4)	5

Values in parenthesis are min-max. [a]According to the Clavien-Dindo classification.

Hepatic recurrence occurred in 17 patients of whom five also had local recurrence at a previously ablated site. Extrahepatic recurrence was detected in 11 patients, all except one in patients with hepatic recurrence. Seven patients underwent re-resection and five were re-

ablated, **Table 14**. All patients who died during the follow-up period (n=10) had hepatic recurrence and eight of them had extrahepatic recurrence.

Table 14. Recurrence patterns and re-resection.

Recurrence patterns and re-resection	n=20
Hepatic recurrence	
Local recurrence	5 (25.0)
New recurrence	17 (85.0)
Extrahepatic recurrence	11 (55.0)
Re-resection for hepatic recurrence	7
Re-ablation of hepatic recurrence	5

Values in parenthesis are percentages.

4.3.1.2 Survival

Ten patients were alive after a median follow-up of 25 months (9-54). Four-year survival in the resected and palliative treated groups were 70% and 4%, respectively. Patients assigned for the MWA strategy had a four-year survival of 41%, a significant difference compared with the palliatively treated group ($p<0.05$).

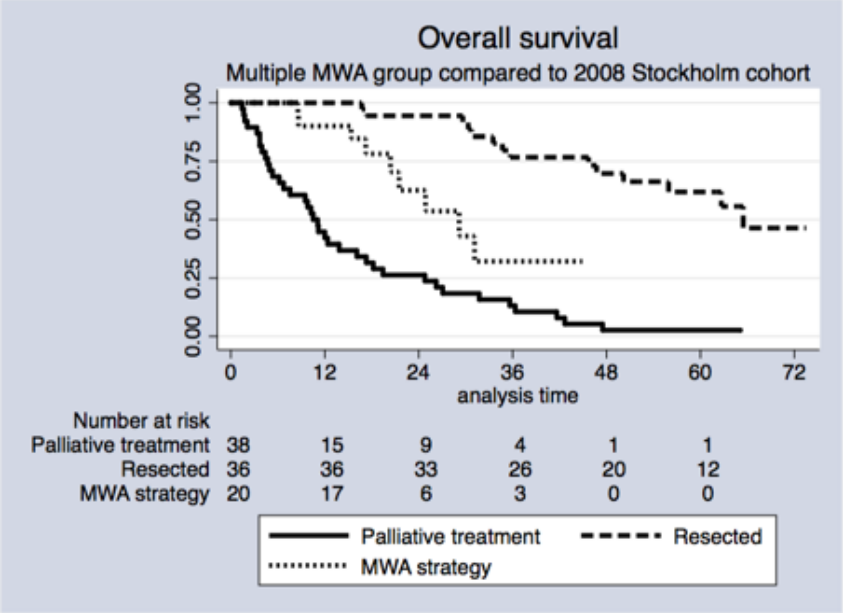


Figure 24. Survival curves in the three studied cohorts

In Cox regression analysis on factors influencing survival, only treatment strategy was significant (MWA versus palliative group, HR 0.56, CI 0.33-0.96). Age, gender, radiological T-stage of the primary tumour, maximum size of metastases, number of metastases and synchronous versus metachronous detection were not significant predictors of survival.

4.4 STUDY IV

From March 2013 to January 2014, 20 patients were enrolled in the study. Due to technical issues, a free-hand insertion technique was used in three patients, and they were subsequently excluded from the performance data analysis. Patient and tumour characteristics for the 17 patients with 25 tumours are presented in **Table 15**. The lesions were located in all segments except segment one.

Table 15. Patient and tumour characteristics for patients included in the study.

Patient and tumour characteristics	Value
Gender (male : female)	13 : 4
Age (year) (±SD)	69.6 ± 9.2
Previous interventions, no. (%) of patients	15 (88.2)
Ablation	7 (46.7)
Resection	1 (6.6)
Ablation and resection	7 (46.7)
No. of previous interventions (min-max)	1 (0-3)
No. of tumours, median (min-max)	1 (1-3)
Tumour type, no. (%) of patients	
Hepatocellular carcinoma	11 (64.7)
Colorectal liver metastases	5 (29.4)
Gastrointestinal stromal tumour metastasis	1 (5.9)
Tumour diameter (mm), mean (±SD)	14.9 ± 5.9
Tumour location depth (mm), mean (±SD)	87.5 ± 27.3
Craniocaudal orientation angle (°), min-max	-1.3 to 26.9
Orbital orientation angles (°), min-max	-30 to 58.2

4.4.1.1 Targeting accuracy

The targeting accuracy was 5.8 ± 3.2 mm with one antenna readjustment. Lateral, depth, and angular errors were 4.0 ± 2.5 mm, 3.4 ± 3.2 mm, and 2.7° ± 2.9°, respectively. No correlation between tumour location depth and targeting accuracy was seen (Spearman ρ=0.2; p=0.3).

4.4.1.2 Safety of the procedure and HFJV

Complications during and after treatment were registered using the Society of Interventional Radiology (SIR) classification (242). Two patients had minor complications none of which were related to the use of HFJV. One patient, treated for a subcapsular tumour, was readmitted for chest wall pain and treated with analgesics (SIR class B complication) and the second patient suffered from a minor skin burn from the MWA antenna (SIR class B complication).

4.4.1.3 Feasibility and radiation dose

Technical failure with the aiming device occurred in three patients, omitting the use of the aiming device. In two patients with tumours located in the lateroposterior section, the angulation of the antenna path was outside the range of the aiming device. After these incidences, patients with tumours in the laterposterior part were placed in a left 45° rotation to enable better access. In the third case, the thread between the carbon plate (placed under the patient, its function being to hold the holding arm) and the holding arm broke. The thread was replaced with a more rigid construction.

Median procedural time was 39.5 min (26-89) for one antenna placement and 70 min (56-126) for two or more antennae placements. Median post-treatment hospital stay was one day (range 1-2 days).

Total radiation dose and interventional dose is outlined in **Table 16**. Two different scanning protocols were used for HCC and liver metastases, which are reported separately.

Table 16. Patient radiation dose

Tumour type	**Radiation dose, mGy x cm, mean (±SD)**
Hepatocellular carcinoma	
DLP_{total}	1154 ± 594
DLP_{inter}	502 ± 326
Liver metastases	
DLP_{total}	597 ± 208
DLP_{inter}	264 ± 121

Dose-length product (DLP). DLP_{inter} corresponds to interventional radiation dose.

5 DISCUSSION

5.1 INCIDENCE OF LIVER METASTASES

The incidence of liver metastases, 26.5%, was found to be lower than often cited but concurrent with other incidence data from previously published population-based studies (50, 51). Approximately half of all patients with liver metastases had liver-only metastases at detection and one third had widespread disease at diagnosis.

5.2 DIFFERENCE IN METASTATIC PATTERN AND SURVIVAL IN MIDGUT VS. HINDGUT CANCER

Patients diagnosed with liver metastases secondary to a midgut cancer had a higher TNM-stage at diagnosis but despite that, CRC originating in the hindgut had a higher incidence of liver metastases. Once liver metastases were detected, the extent of segmental involvement and number of metastases were more pronounced in midgut cancer. Lung metastases were more often diagnosed in hindgut cancer and peritoneal metastases more often in midgut cancer. This study also confirms the higher proportion of liver metastases among younger patients, potentially attributable to both patient and doctor delay. Reports on whether incidences of liver metastases are dependent on primary tumour location are inconsistent. Two studies, one German and one study based on data from the Surveillance, Epidemiology, and End Results (SEER) database showed a higher incidence of liver metastases in colon cancer as compared to rectal cancer. However, the German study (56) only included patients with synchronously detected liver metastases in surgically treated CRC and the SEER data base is limited to metastases registered at the time of CRC diagnosis (58). In another study by Lee et al., no difference in hepatic spread was detected (59). In a Norwegian study that also only included curatively treated CRC patients, left-sided colon cancer was found to be associated with an increased risk of metastatic spread to the liver (60).

OS was significantly lower in patients with liver metastatic midgut cancer compared with hindgut cancer. This is in keeping with other reports of inferior survival of right-sided colon cancer in the presence of metastatic disease (103, 243, 244). Many reports on the subject focus on potential differences in survival between right-sided and left-sided cancer in non-metastatic CRC, and also in this respect, contradictory data is reported. A recently published meta-analysis showed that right-sided cancer was a significant risk factor for death in Western countries, making lifestyle, health-care utilization, and genetic background potential factors contributing to the issue (43). A more advanced tumour stage was seen in patients with midgut cancer, which is in agreement with other publications (42) and potentially mirrors later diagnosis of right-sided cancer and consequent lead-time bias. To investigate mortality by stage, Weiss et al. adjusted for multiple patient and tumour factors and evidently found no overall difference in five-year mortality between right- and left-sided colon cancer. However, the study was limited to stage I-III and only curatively resected patients were included. In a subgroup analysis of stage III disease, right-sided cancers had a shorter survival (245). The SEER data base was yet again used when Meguid et al. found a persistent

significant difference with a 5% increased mortality risk in right-sided colon cancer when controlling for multiple factors, including stage (246). Patients with right-sided cancer have been found to be older (43) and suffering from more comorbidities (247) and, consequently, these patients are not treated with adjuvant chemotherapy to the same extent. Since the incidence of right-sided cancer is increasing, these results might have clinical implications. It is likely that there are differences in oncological outcome based on tumour location since right-sided cancer is associated with high MSI and CpG island methylation, whereas left-sided cancer more often shows chromosomal instability, factors known to affect the success of chemotherapy regimens.

The present study failed to show any survival difference between midgut and hindgut cancer in the overall cohort, only among patients with liver metastases.

5.3 SURVIVAL IN METASTATIC COLORECTAL CANCER

Patients with lung-only metastases had a three times longer median survival than patients with liver only metastases and in proportional hazard regression analysis, the presence of lung metastases did not influence OS, neither in the entire cohort nor among patients with simultaneous liver metastases. In patients with liver metastases lung metastases are known to be associated with better outcome compared with other extrahepatic sites (167). Based on these results, one could speculate on the benefit of performing liver resections on patients with concomitant unresectable lung metastases. In a report by Dave et al., patients scheduled for resection of liver and lung metastases, who for some reason never underwent resection of lung metastases (due to progression of lung metastases or recurrent liver metastases) still had a five-year survival rate of 30% (248). Andreas and colleagues found that patients with simultaneously diagnosed liver and lung metastases, and resected for both metastatic sites, had a similar OS to those who had undergone resection of isolated liver metastases (123). The survival was found to be even greater in patients resected for liver plus lung metastases as opposed to patients who underwent resection of liver-only metastases (122). Contradictory results are presented by Nordholm-Carstensen in a large Danish nationwide study where the occurrence of synchronous lung metastases had a profound impact on survival (249).

5.4 THE IMPACT OF A LIVER MULTIDISCIPLINARY TEAM CONFERENCE

Several publications have, in different ways, emphasized the importance of a dedicated hepatobiliary team in the management of liver metastatic CRC in terms of higher resection rate and improved DFS and OS (72, 74-76). Study II differs from previous publications since the re-evaluations were done on all patients with liver metastases originating from a population-based cohort, including patients with extrahepatic metastases and accounting for comorbidity and patient's own preferences towards treatment.

Twenty-two patients (12.9%) that had not been assessed by a hepatobiliary surgeon were assessed as resectable/potentially resectable at the fictive liver MDT. Two were assessed by a medical oncologist only and three were managed by a colorectal surgeon outside a colorectal MDT, the remaining seventeen were evaluated at the colorectal MDT as having unresectable

liver metastases. These twenty-two patients were older and a larger proportion had five or more liver metastases compared with those referred to the actual liver MDT, but they did not differ in ASA grade. One must though bear in mind the possibility of other factors not clearly identified in study II that would have limited the number of these patients that eventually would have undergone surgery. Consistency in decision-making in patients considered resectable/potentially resectable and not resectable at the actual and fictive liver MDT were evaluated with Cohen's kappa, measuring the interrater agreement to 0.83, which is considered acceptable.

In a study by Young et al., management decisions differed between colorectal and liver specialists in almost 50% of patients (81). Decision-making by non-liver surgeons was evaluated by Jones et al., who found that almost two-thirds of patients, treated with palliative chemotherapy, were assessed as potentially resectable by a group of experienced liver surgeons (250). The Jones study was limited to patients treated with palliative chemotherapy and liver-only metastases and in the study by Young et al., only radiology was re-evaluated. Thillai et al. reported that a third of patients with liver-limited diseases were never referred to a liver MDT (251).

The re-evaluated population of study II were generally well treated with high referral rates and resection rates to start with. Despite that, an additional 22 patients were found resectable/potentially resectable resulting in a hypothetical resection rate of nearly 40%.

Liver imaging was non-diagnostic for 17.7% of the re-evaluated patients, referring solely to liver imaging. Mostly, other factors such as resectablilty of the primary tumour, the extent of extrahepatic metastases or comorbidity nevertheless made decision-making possible. In a few cases, MRI without liver-specific contrast and diffusion-weighted imaging, only displaying a small number of metastases was considered as resectable even though it would not have been sufficient for a decision in 2017, when state-of-the art MRI is almost mandatory.

5.5 VARIATIONS IN REFERRAL PRACTICE TO A LIVER MULTIDISCIPLINARY TEAM CONFERENCE

Factors found to be associated with referral were age, ASA score and number of liver metastases, similar factors identified by Ksienski et al. (252).

Referral rates varied between hospitals (0-48 %) in study II, a seemingly large difference but statistically non-significant. Marked differences in referral practice are seen in numerous other studies (74, 80, 81, 252). Economic and resource constraints, local medical expertise, lack of physician engagement and time, have all been identified as barriers for proper referral (77). Since no clear guidelines exist to facilitate the assessment of referral to a liver MDT, in the worst case, referral might be dependent on the treating physician's knowledge on updated resection criteria. Differences in referral rates could also be explained by factors other than type of hospital, such as patient co-morbidity, patient preference and the arrangements around multidisciplinary team meetings.

5.6 FEASIBILITY OF A MULTIPLE ABLATION STRATEGY

The multiple MWA approach in study III, including re-resection and re-ablation, rendered a group of patients tumour-free with major complication rates of 25%. The four-year OS in the multiple MWA group was significantly better than the historic group treated with palliative chemotherapy.

Thermal ablation (RFA) has been shown to be inferior to resection (227-229) but is better than palliative chemotherapy alone regarding survival (148, 221). The concept of study III highlights ablation as an alternative first-line treatment strategy in patients with potentially resectable or unresectable metastases. In patients with a high risk of recurrence (multiple lesions and synchronously detected metastases) major resections may render further interventions impossible due to limited technical options. By adopting a multiple ablation strategy, all treatment options including resection and re-ablation are still available. Recurrence rate after liver resection is reported to range from 56.7 to 63% within two years (85). In study III, 17 patients (85%) had intrahepatic recurrence within the follow-up period of which 12 were re-resected or re-ablated.

In study III, MWA was performed during open surgery which has numerous advantages compared with a percutaneous approach. Antenna placement can be done from a wide range of angles and be further facilitated by liver mobilization. Concomitant liver resections can be performed and when ablating sub-capsular lesions, distancing of adjacent organs is easily done. Still, with reliable image-guidance technique, the laparoscopic approach is desirable and important for future development. Computer-assisted navigation, not requiring real-time visualization of lesions, was used in seven of the 20 patients in study III, demonstrating its feasibility.

5.7 TARGETING ACCURACY IN STEREOTACTIC PERCUTANEOUS MICROWAVE ABLATION

Antenna placement accuracy was slightly poorer in study IV related to other reports on the use of similar systems. Improved accuracy is to be expected as experience increases. An optical-based navigation system was utilized by Widmann et al. with a mean lateral error of 3.6 ± 2.5 mm (218) compared with 4.0 ± 2.5 mm in study IV. Mbalisike used a robotic guidance system and compared it with manual guidance and achieved a significant improvement in applicator position with the robotic system (5.3 mm $\pm$ 1.8 mm and after manual readjustment; 1.9 ± 1.7) (216). Another robotic system was used by Beyer et al., with improved accuracy compared with manual antenna insertion (3.1 ± 2.5 mm and after manual correction; 1.6 ± 1.3) (215). Notably, in both studies, manual correction was required to attain desired accuracy. Electromagnetically tracked antennae were used by Krücker which improved the tracking error to 2.7 ± 1.6 mm (217). A low number of repositions of the antenna is desirable because of less need for repeated control scans, resulting in a reduced radiation exposure, and less insertion-related injuries. Longitudinal error is of minor importance in the clinical setting since further insertion or withdrawal of the antenna is easy

and does not require antenna replacement. The low antenna readjustment rate and seemingly larger target error of study IV perhaps reflect the study conductors' acceptance of a larger error at the expense of an increased ablation zone.

5.8 FEASIBILITY OF STEREOTACTIC MICROWAVE ABLATION

Two minor complications occurred during study IV and no complications related to the use of HFJV. Technical error occurred during three procedures, omitting the use of the aiming device. Since the study included the first 20 patients on whom the system was used, technical failure is to be expected and did not happen at the expense of patient safety.

The CT protocols for HCC and metastases were different since detection of HCC requires imaging during three contrast phases and hence was reported separately. For the group with metastases, the mean DLP_{inter} was 264 ± 121 mGy × cm, whereas for the group with HCC, it was 502 ± 326 mGy × cm. This is in range with CT fluoroscopy-guided RFA/MWA of liver tumours used by Kloeckner et al., thus without computer or robotic guidance systems (253). Abdullah et al. used a CT-guided robotic positioning system, and demonstrated a 30% reduction in radiation dose per lesion, compared with the standard ablation procedure without the assistance of the robotic device. The difference was however not statistically significant (254). CT hardware, with expected annual updates, and protocols varies substantially between institutions, making a comparison of radiation dose between different studies unreliable and irrelevant.

The procedural time, wide angular range of antenna insertion, different tumour location depth and tumour locations in all segments but segment one, all indicate the feasibility of the system used in study IV.

Antenna placement accuracy is sometimes hampered by breathing-associated liver motion. Respiratory motion control in percutaneous ablation/biopsies is often achieved by disconnecting the airway tube from the ventilator at end expiration. Denys and colleagues used HFJV for percutaneous tumour ablation and measured a target movement of less than 3.75 mm (slice thickness) (241). Conventional ventilation was compared with HFJV in percutaneous RFA of liver tumours and the latter was associated with a significant reduction in radiation (255). Biro et al. observed a 75% reduction in liver movement in a patient who underwent RFA of multiple liver tumours (256). Only the safety of HFJV was an endpoint in study IV, but its appealing characteristics warrant further evaluation in the clinical setting.

5.9 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

5.9.1.1 Precision

Assessing the accuracy of a study is done by evaluating its precision and validity. Precision mainly depends on sample size and random errors. It is most often expressed by confidence intervals; the wider the CI, the poorer the precision. Sample sizes of studies I and II are small and not based on power calculations. Study I was designed as a descriptive study and study II

aimed to evaluate the decision-making process where the time-consuming process of re-evaluating imaging and patients in the setting of a fictive MDT was a limiting factor. There was also an ethical aspect of study II where we wished to minimize re-evaluation of any live study participants. Random errors occur in most studies and since they occur randomly, they do not tend to cause a false association. Random errors cannot be corrected for in a statistical analysis.

5.9.1.2 Validity and systematic errors

Validity is divided into external and internal validity where the former refers to its generalizability and whether the results of the study can be used in other populations and is dependent on the internal validity. The internal validity addresses the question "Does the study measure what it was intended to" and is dependent on different types of bias (systematic errors). *Selection bias* occurs when the selection of study participants is incorrect and non-representative. *Information bias*, also called misclassification, is subdivided into non-differential and differential misclassification. *Differential misclassification* is non-random and can cause a false association. *Non-differential misclassification*, on the other hand, is random and usually dilutes the estimates toward the null (bias towards the null). *Confounding* is a factor associated with the outcome and exposure but not an intermediate link between exposure and outcome. Confounding can be adjusted for in numerous ways (randomization, restriction, stratifying, regression analyses etc.). Residual confounding is often present because of unknown confounders not adjusted for.

Study I was a descriptive, population-based study based on the SCCR. The SCCR is a prospectively maintained database with confirmed high validity (5). Not all data required for studies I, II and III were available in the SCCR and acquiring all relevant data required a review of electronic patient records. When collecting the additional data, it is possible that information bias, most likely in the form of non-differential misclassification, was introduced in the data. This error could have been reduced by only using information from large validated registries. By only including patients from the greater Stockholm region, it might limit the external validity of studies I and II. Based on the results from Norén et al. (102, 103), with Stockholm having a higher resection rate of liver metastases and not suffering from any gender discrimination in treatment of liver metastatic disease compared with the rest of Sweden, the generalizability of studies I and II could be questioned.

A potential difference between midgut and hindgut cancer in study I was a hypothesis created "a posteriori", hence the lack of variables interesting for that particular question such as mutation status. Since right-sided cancer is reported to be diagnosed at a later stage, adjusting for stage should have been done when assessing differences in right-sided versus left-sided cancer. Furthermore, various definitions exist in the literature in trials comparing right and left colon cancer on whether to include rectal tumours or not. In study I, rectal cancer was included and a comparison with previous literature might therefore be limited. Also, not adjusting for ASA grade in study I is a major limitation and most likely an important confounder. Adjusting for the administration of chemotherapy is complex. Major

improvements and changes in the indication for chemotherapy have occurred since 2008, this being the main reason why chemotherapy was not adjusted for.

Expectation bias is when the researcher allows his or her expectations to affect the outcome of a study. This is of major importance in study II where the authors of the manuscript also constituted the fictive conference and were naturally not blinded to the hypothesis of the study. It is possible that the conference participants decided in favour of resection more often than would have been the case in an actual setting. Using Cohen's kappa is thought to be a more accurate measure of interrater agreement than just percentage agreement calculation since κ takes the possibility of the agreement occurring by chance into account. Kappa values over 0.75 are interpreted as excellent agreement. A way to further highlight any overestimation, and something that in retrospect could have been done, was to re-present randomly chosen cases at the fictive conference to see if the same fictive decisions were made. Study II lacked the power to detect any potential differences in referral rate. Another reservation about the study design of study II is the absence of specific competence within the fictive liver MDT, for example a thoracic surgeon, to decide on the resectability of pulmonary metastases.

In study III it is possible that some of the patients included in the multiple ablation strategy group would have been considered as potentially resectable with more established combination methods in other institutions. Selection bias, as in selecting patients with potentially other favourable factors affecting survival, is almost always present in these kinds of studies. We have already passed the line where it is ethical to randomize unresectable patients into treatment with thermal ablation or not. Perhaps propensity score analysis is the best way to truly evaluate the benefit of thermal ablation.

When analysing survival in study III, the numbers at risk after 36 months are low and should be interpreted with caution. Additionally, comparing cohorts from different time-periods, as is the case in study III and to some extent study II, always introduces bias since treatment algorithms, medication, surgical technique and indications continuously evolve. In study III, the palliative group treated with chemotherapy only, was selected solely based on imaging findings with tumour criteria corresponding to being treatable with MWA. It is likely that these patients had contraindications precluding resection and therefore constitute non-comparable groups.

As a feasibility study, study IV had restrictive inclusion and exclusion criteria and consequently an impaired external validity. Study IV does not provide any results on local tumour progression or any survival data. Navigation systems have obvious theoretical advantages over conventional US or CT guidance, but in order to establish their true impact on targeting accuracy and survival outcomes, comparative studies need to be done. An additional limitation in evaluating irradiation in study IV was the use of DLP rather than measured absorbed doses of the patients.

6 CONCLUSIONS

Study I

- Twenty-six percent of CRC patients develop liver metastases of which two thirds are synchronously detected.
- Patients with liver metastatic midgut cancer had significantly worse OS compared to liver metastatic hindgut cancer.
- Hindgut cancer had a higher incidence of liver metastases and lung metastases while midgut cancer had a higher incidence of peritoneal carcinomatosis.
- The results from study I add to the ongoing research results showing clinical differences between right- and left-sided colon cancer.
- OS was not influenced by the presence of lung metastases in patients with CRC.

Study II

- A meaningful number of patients with resectable/potentially resectable liver metastases were not evaluated in the setting of a liver MDT conference.
- Referral rates to the liver MDT conference did not differ significantly between hospitals in the Stockholm region.

Study III

- In highly selected patients a multiple ablation strategy offers survival benefits compared to palliatively treated patients.
- The majority of patients treated with multiple ablations suffer from both intra- and extrahepatic recurrence.

Study IV

- CT-guided stereotactic navigation for percutaneous MWA provides sufficient accuracy and is technically feasible with an acceptable radiation dose.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Tjock- och ändtarmscancer är den tredje vanligaste cancerformen i världen och Sverige. Varje år får cirka 4000 personer tjocktarmscancer i Sverige och motsvarande siffra för ändtarmscancer är 2000 personer. Tjocktarmscancer är lika vanligt hos män och kvinnor medan ändtarmscancer är något vanligare hos män. Tjock- och ändtarmscancer är framförallt en cancerform som drabbar den äldre befolkningen (över 65 år) och fem-årsöverlevnaden beräknas vara 61% för män och 65% för kvinnor.

Sjukdomen kan sprida sig till andra organ, och vanligast är dottertumörer till levern vilket sker hos en dryg fjärdedel av alla patienter. Historiskt sett har prognosen för patienter med dottertumörer i levern varit dyster men tack vare utvecklingen av kirurgiska metoder och cellgifter så kan idag en fjärdedel opereras vilket resulterar i en 5-årsöverlevnad på upp till 50%. Cellgifter kan förlänga livet hos en person med spridd cancer till levern men operation av dottertumörerna är det enda som är botande. Förutsättningen för att en operation ska kunna utföras är att det inte finns för många dottertumörer och att de inte är alltför spridda i levern.

Omhändertagande av patienter med spridd cancer till levern ska ske inom ramen för en multidisciplinär terapikonferens där både leverkirurger, onkologer, radiologer och patologer deltar. Detta för att säkerställa att den mest optimala kombinationen av kirurgisk och onkologisk behandling erbjuds. Det har visat sig att om patienter med dottertumörer i levern bedöms av ett team med en leverkirurg så opereras fler och därmed så kan fler patienter botas. Tidigare studier har dock visat att långt ifrån alla patienter med dottertumörer i levern erbjuds operation och det finns stora skillnader mellan sjukhus i olika regioner när det gäller hur många som opereras för sina dottertumörer i levern.

Mindre tumörer i levern, som av en eller annan anledning inte kan opereras bort, kan ibland förstöras med värme (radiofrekvensbehandling och mikrovågor). Den förmodat effektivaste tekniken är mikrovågor och innebär att en nålliknande antenn förs in i tumören och den värme som bildas omkring antennens spets förstör tumörvävnaden. Metoden kan bara användas på mindre tumörer och är inte bevisat lika effektiv som operation för dottertumörer. Levercancer är en cancerform som uppstår direkt i levern och för dessa tumörer är mikrovågor/radiovågor likvärdigt med operation. Utmaningen med värmebehandling är att lyckas föra in antennens spets till tumörens centrum. Detta görs med olika rikthjälpmedel; ultraljud, datortomografi eller GPS-liknande system. Alla tumörer är inte synliga med ultraljud och användandet av enbart datortomografi kan ge onödigt hög stråldos till både patient och sjukvårdspersonal.

Denna avhandling består av fyra studier som alla berör olika aspekter av patienter med dottertumörer i levern; hur vanligt det är, hur överlevnaden ser ut, betydelsen av den multidisciplinära terapikonferensen och behandling med mikrovågor när operation inte går att utföra. **Studie I** syftade till att beskriva spridningsmönstret av dottertumörer hos patienter med tjock- och ändtarmscancer. Alla patienter som diagnostiserades med tjock- och ändtarmscancer i Stockholmsområdet under 2008 identifierades och följdes under 5 år.

Dottertumörer i levern påvisades hos 26.5% (272 patienter av 1026 med tjock- och ändtarmscancer). Spridning till lever och lungor var vanligare hos de med vänstersidig tjocktarmscancer och ändtarmscancer jämfört med de som hade högersidig tjocktarmscancer. Dock hade de med högersidig tjocktarmscancer fler dottertumörer i levern när de väl spridit sig dit och överlevnaden var betydligt sämre jämfört med patienter som hade vänstersidig cancer. Dessa resultat kan ha betydelse för hur patienter ska följas upp och belyser att det troligen finns molekylära och immunologiska skillnader mellan höger- och vänstersidig tjocktarmscancer. Spridning av dottertumörer till lungorna verkade inte påverka överlevnaden vilket är intressant eftersom patienter med dottertumörer i lungorna tidigare inte opererats då de ansetts ha en alltför spridd sjukdom.

Syftet med **studie II** var att undersöka hur många som skulle kunna bli opererade för sina dottertumörer om alla bedömdes av en multidisciplinär terapikonferens med en leverkirurg närvarande. För att undersöka detta skapades en fiktiv konferens där alla patienter med dottertumörer i levern från **studie I** eftergranskades och ”nya” beslut fattades, oberoende av tidigare behandlingsbeslut. Från **studie I** hade vi sett att 102 (37.5%) patienter remitterades till leverkirurgisk terapikonferens men att resterande 170 patienter aldrig bedömdes av en leverkirurg. På den fiktiva konferensen bedömdes att ytterligare 22 patienter (12.9%) av de 170 patienterna kunde ha opererats. Detta skulle innebära att under optimala förhållanden så borde närmare 40% av alla med dottertumörer i levern kunna opereras till skillnad från den faktiska siffran på cirka 25% från **studie I**. Denna studie betonar hur viktigt det är att alla med spridd tjock- och ändtarmscancer bedöms på en leverkirurgisk terapikonferens.

I **studie III** inkluderades 20 patienter vars dottertumörer i levern inte gick att operera bort på grund av alltför omfattande spridning i levern. Syftet var att behandla dessa patienter med mikrovågor under öppen operation och utvärdera genomförbarheten och säkerheten med ett sådant tillvägagångssätt. Överlevnaden i studiegruppen jämfördes med de patienter från **studie I** som opererats och en grupp från **studie I** vars tumörer var jämförbara med de i **studie III** (till antal och storlek) men som i verkligheten enbart behandlades med cellgifter. Gruppen som värmebehandlades med mikrovågor hade mellan 4 och 22 dottertumörer och en fyra-årsöverlevnad på 41% att jämföra med 70% hos den historiska gruppen som opererades och 4% för de som enbart fick cellgifter. Dock hade arton av 20 patienter återfall av tumörer i levern och nio patienter drabbades av behandlingskrävande komplikationer relaterade till värmebehandlingen. Slutsatsen blir att det går att utföra värmebehandling med mikrovågor av många dottertumörer med vad som verkade vara en överlevnadsvinst jämfört med historiska material. Vidare studier med längre uppföljning och bättre jämförelsegrupper krävs dock för att utvärdera denna behandlingsstrategis plats hos patienter med många dottertumörer som inte går att operera bort.

Bakgrunden till **studie IV** är att lokal värmebehandling har en hög återfallsfrekvens av tumörer vilket förmodligen beror på att storleken på området med tumördöd inte går att förutsäga tillräckligt exakt och att metoderna för att placera antennen centralt i tumören inte är precisa nog. För att öka precisionen har olika navigationssystem utvecklats. Tekniken

bygger på att bilder tagna i en datortomograf före operationen sammanfogas med en GPS-liknande datorstyrd navigering varvid levertumörerna kan identifieras utan att man behöver öppna buken. Denna teknik hade innan start av **studie IV** visat sig fungera i modeller men var inte utvärderad på människor. Tekniken användes dock sedan tidigare vid öppen operation, det var bara kopplingen till röntgenbilderna som ännu inte var testad annat än i modeller.

Syftet med **studie IV** var att utvärdera navigationssystemet för guidning av antennen vid värmebehandling med mikrovågor av tumörer i levern. Tjugo patienter med levercancer och dottertumörer från tjock- och ändtarmscancer inkluderades i studien. Tumörerna hos dessa patienter var inte synliga med ultraljud, det rikthjälpmedel som vanligast används när antennen ska placeras genom huden, och gick heller inte att operera bort. Antennens läge i relation till tumören, ingreppets stråldos, säkerhet och genomförbarhet utvärderades. Resultatet från studien var att antennen placerades i genomsnitt 5.8 mm från det tänka målet, viket är en acceptabel felmarginal. Stråldosen för varje patient var jämförbar med andra liknande studier och metoden hade en låg komplikationsfrekvens.

Navigationssystemet används nu i klinisk vardag på Danderyds sjukhus för att placera mikrovågsantennen i tumörer när ultraljudsledning inte går att använda. Huruvida navigationssystemet ger en bättre precision än andra riktmedel (ultraljud och datortomografi), och i förlängningen färre tumöråterfall och därmed potentiellt längre överlevnad, återstår att visa.

8 FUTURE PERSPECTIVES

Study I was mainly hypothesis generating and invites further studies on potential differences between midgut and hindgut cancers in metastatic disease and the pathogenesis behind it on a molecular level. This might influence and assist in more structured and individualized guidelines for follow-up routines. The impact of lung metastases on survival in CRC is another interesting subject, especially since the criteria for resectability are continuously expanding. Perhaps, unresectable lung metastases should not be considered an absolute contraindication for resection of liver or other extrahepatic metastases. The nature of population-based registries in Sweden could enable study designs that may answer some of these questions.

Surgical techniques, chemotherapy options and perioperative care are continuously evolving and will result in further increased resection rates for CRCLM and hopefully improved survival. Ensuring that all potentially resectable patients are worked up with state-of-the art imaging and evaluated by a liver MDT should be key priorities. Referral of all patients with CRCLM may not be practical and affordable. If a selective referral policy is applied, it should be clear and to some point be regulated. It should be supported by education of gastroenterologists, medical oncologists and general and colorectal surgeons.

A main focus for the liver research group at Danderyd Hospital is to further develop and validate the role of MWA in the treatment of CRCLM. Since the start of thermal ablation at Danderyd hospital, a prospective database with information on all patients and procedures has been maintained. This could serve as robust data to describe recurrence pattern, depending on tumour characteristics and interventional technique and access used. It will also be possible to generate long-term survival data.

Microwave Ablation Versus Resection for Resectable Colorectal liver metastases (MAVERRIC) is an ongoing study aiming to prove that first line local ablation of CRCLM with MWA is not inferior to liver resections in a subset of patients in terms of survival rates, complication rates and need for further interventions. Patients that are resectable and have tumours of 30 mm or less and not more than five in number, and deemed as possible to ablate as well as resect, are offered treatment with an ablative strategy using state of the art navigation and MWA devices. The study cohort will be compared to controls from the Swedish liver registry using propensity score analysis.

Estimating a correct ablation volume is crucial in reducing local recurrence rate and thermal induced injuries to adjacent structures and organs. The research group is planning to perform a study to quantify the post-ablation margins of patients that have undergone percutaneous navigated ablation of the liver to see which factors influence ablation volume to enable more accurate prediction of ablation volumes. Factors that could influence ablation volume, beside applied time and energy, include tumour type (hypervascular versus hypovascular tumours) and tissue elasticity or fibrosis, affected by underlying liver disease and chemotherapy.

Continuous development of the computer-assisted navigation system with software improvements and EM tracking of the antenna, both for percutaneous, laparoscopic and open surgery use, will need evaluation in the form of controlled studies.

9 APPENDIX

9.1 A. PATIENT INFORMATION AND CONSENT FORM FOR STUDY IV

Valideringsstudie av datorstyrd navigering av ablationsnålar för behandling av levertumörer.

Bakgrund och syfte: Detta är en vetenskaplig studie som syftat till att förbättra omhändertagandet av patienter med tumörer i levern som skall behandlas med mikrovågsablation.

Idag används ultraljudsapparat för att under operationen kunna lokalisera tumörförändringar inne i levern, förändringar som ofta inte syns eller känns från leverytan. Det medför att behandlingen oftast måste göras under narkos på operation med en öppen buk och blottad leveryta.

Det finns nu en ny teknik där man kan använda bilder tagna i datortomografi före operation, där man med hjälp av små plastkulor som tillfälligt limmas på huden nära levern, med en gps-liknande datorstyrd navigering kan hitta levertumörerna utan att behöva öppna buken. Denna teknik har visat sig fungera alldeles utmärkt i modeller men är inte utvärderad i kliniskt bruk. Däremot är navigeringsutrustningen och tekniken för att bränna levertumörer väl dokumenterad och i kliniskt bruk. Det är bara kopplingen till röntgenbilderna som ännu inte är testad annat än i modeller.

Förfrågan om deltagande: Du är nu tillfrågad att vara med i denna studie för att se om denna teknik är bra och kan göra att man kan behandla levertumörer med mindre invasiv teknik, för att minska smärtor och förkorta vårdtider. Du tillfrågas eftersom du remitterats till Danderyds Sjukhus för mikrovågsbehandling av levertumörer.

Hur går studien till? Behandlingen utförs i narkos. Innan operationen limmar man fast några små plastkulor på skinnet kring höger revbensbåge och därefter gör en ny datortomografi strax innan behandlingen som utförs i datortomografen på röntgen. Under behandlingen kommer dina tumörer att behandlas på samma sätt som vi annars gör, det vill säga med hjälp av mikrovågor, men i och med att du har hudmarkörer och en färsk datortomografiundersökning så kan vi utvärdera om det hade gått lika bra att göra med den nya tekniken, innan mikrovågsbehandlingen inleds säkerställs att nålen ligger mitt i tumören med hjälp av en riktad datortomografiundersökning. När operationen är klar är ditt deltagande i studien klar.

Biobanksprover: Inga vävnadsprover tas tillvara för lagring i biobank.

Vilka är riskerna? Denna forskningsstudie innebär två extra riktade datortomografiundersökningar med lägre stråldos än en vanlig datortomografiundersökning av levern. Denna stråldos motsvarar mindre än 30 års naturlig bakgrundsstrålning i Stockholm, vilket är en liten stråldos.

Finns det några fördelar? Deltagande i studien kan innebära fördelar då det med den nya tekniken i vissa fall går att behandla utan öppen operation med de risker ett stort buksnitt har. Dessutom görs behandlingen på alldeles färska röntgenbilder vilket i enstaka fall kan innebära att man hittar en ytterligare tumör som går att behandla samtidigt.

Hantering av data och sekretess. Uppgifter om navigationsutrustningens precision avseende placering av mikrovågsnål i tumörerna kommer att sparas i en datoriserad forskningsdatabas tillsammans med uppgifter om tumörernas storlek och lokalisation, samt uppgifter om tidsåtgången för de olika momenten vid behandlingen. Personnummer kommer inte att ingå i databasen. Databearbetningen kommer delvis att genomföras tillsammans med den forskargrupp i Schweiz som tagit fram navigationsutrustningen. Dina svar och dina resultat kommer att behandlas så att inte obehöriga kan ta del av dem. Forskningsresultaten kommer sedan att presenteras i form av en vetenskaplig artikel där enskilda forskningspersoner inte går att identifiera.

Hur får jag information om studiens resultat? Du får resultaten av din behandling innan hemskrivning från sjukhuset, oftast dagen efter behandlingen. Om du önskar kan du få en kopia av det slutgiltiga forskningsresultatet när studien är färdig.

Försäkring, ersättning. Det normala försäkringsskyddet för behandlingar i sjukvården ingår, den så kallade patientskadeförsäkringen. Ekonomisk ersättning utgår inte annat än befrielse från patientavgiften.

Frivillighet. Du har självklart rätt att när som helst utgå ur studien. Ditt deltagande i studien är helt frivillig och påverkar inte din vård på annat sätt än vad som ovan beskrivits.

Ansvariga:

Jennie Engstrand, läkare, Kirurg- och Urologkliniken Danderyds Sjukhus

Jacob Freedman, överläkare, docent, Kirurg- och Urologkliniken Danderyds Sjukhus tel. 08-123 58119

Henrik Nilsson, bitr öl, med dr, Kirurg- och Urologkliniken Danderyds Sjukhus

Eduard Jonas, överläkare, docent, Leverkirurgiska sektionen, Karolinska Universitetssjukhuset i Huddinge

Samtyckesformulär

Härmed intygas att jag har informerats, fått tillfälle att ställa frågor, fått dem besvarade och samtyckt till deltagande i studien.

_____

Underskrift

_____

Namnförtydligande

_____

Personnummer

_____

Kodnummer (ifylles av forskningsansvarig)

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