Resection rates and predictors of survival after surgery for colorectal liver metastases

Jon-Helge Angelsen

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Author: Jon-Helge Angelsen

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Scientific environment

The work presented in this thesis is carried out at the Department of Acute and Digestive Surgery, Haukeland University Hospital, Bergen and through the PhD-programme at the Department of Clinical Medicine (K1), Faculty of Medicine, University of Bergen, Norway.

The research has been conducted in collaboration with the Department of Oncology and Centre for clinical research, Haukeland University Hospital.

Parts of the data acquisitions have been conducted in collaboration with the Norwegian Patient Registry and the Cancer Registry of Norway.

To Karianne, Cornelia, Erica and Nathaniel

Acknowledgements

As a newly employed resident at Haukeland University Hospital and with three year surgical experience, I was in 2007 introduced to patients with colorectal liver metastases (CLM) treated with different evolving therapeutic modalities. My curiosity led me to several questions that I found important to investigate further: what determine the survival rates? When should patients be recommended for inclusion to surgery for CLM? Where do we strike the balance between the aggressiveness against the metastases, and the misery imposed through surgical overconfidence in borderline cases? By the guidance of skilled and friendly mentors and colleagues, a project was initiated, and the result is this PhD thesis.

A number of persons have been of great assistance towards the completion of the thesis. First I want express my gratitude to my supervisor Professor **Asgaut Viste** for his encouragements and support, and systematic and constructive feedback during data acquisition and the writing process. My co-supervisor Dr. med. **Arild Horn,** opened the door into this project and let me establish a local database for CLM patients. I am also very thankful for the supervision through the writing process and for some hundred hours with HPB apprenticeship in the operating theatre spiced up with humour and anecdotes.

Combining research and clinical work around the clock might be challenging. I will therefore thank department manager **Janiche B. Heltne** and head of upper GI section PhD **Dag Hoem** for facilitating and encouraging me throughout this process. Also thanks to Dag Hoem for support and constructive contribution as a co-author of paper II.

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I am also very thankful to the patient permitting me to use their data in this work. Hopefully, some of them – and future patients – will benefit from the research contained in this thesis.

Finally, I want to thank my family for the great support and encouragement. My warmest thanks go to my parents in Lofoten, **Jon** and **Haldis** for their continued interest and love towards both me and my family. My precious children **Cornelia Angelina**, **Erica Isabella** and **Nathaniel August** are constant reminders of what matters in life. They bring so much fun and energy to our home, and are a welcomed "distraction" from my work. And last but certainly not least, a heartfelt gratitude to my wife **Karianne** for her patience, loyalty and love, taking more than her fair share of domestic duties during my long periods of work. This thesis is dedicated to you.

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Abstract

Introduction:

Occurrence of liver metastases is common following colorectal cancer (CRC), and resection is the only option with a potential for cure offered to a minor part of these patients. During the last decades there have been major improvements in the oncosurgical treatment, along with expansions in inclusion criteria for surgery. The majority of the patients will unfortunately experience post-resection recurrence. Divergent results have been presented regarding the need of clear resection margins (RMs) to accomplish an optimal outcome. Data on national resection rates in patients with CLM are sparse.

Aim of the thesis:

I: To study RMs and the correlation with local recurrence (LR) pattern, time to recurrence (TTR) and overall survival (OS) in patients resected for CLM.

II: To study patterns of recurrence, and post-recurrence survival (PRS) according to sites of recurrence following resection for CLM.

III: To study resection rates in patients diagnosed with CLM in Norway, focusing on characteristics like age, geographical regions and primary tumour.

Methods:

Paper I and II are based on a combined retrospective (1998-2008) and prospective (2009-2012) retrieved database of consecutive patients treated with resection for CLM at Haukeland University Hospital. Paper III is based on synchronized data from the Norwegian Patient Registry (NPR) and the Cancer Registry of Norway (CRN) where patients with a diagnosis of CRC (ICD-10: C18-20) and liver metastases (C78.7) were

enrolled (2011-2013). Cumulative resection rates (CRR) following CLM were retrieved from any registration of hepatic resection (NCSP: JJB) in the data set. TTR, OS and CRR (paper I-III) were obtained using Kaplan Meier method with Log-rank test (univariate) and COX regression analysis (multivariate). All the studies were accepted by the Regional Committee for Medical and Health Research Ethics (REK-Vest).

Results:

A total of 242, 311 and 2960 patients were enrolled in paper I, II and III, respectively. In paper I the patients were grouped according to the width of the resection margins; <1 mm/R1 (n = 48), 1 to 4 mm (n = 77), 5 to 9 mm (n = 46) and ≥10 mm (n = 71). LR was significantly higher in patients with RM < 5 mm. A significant difference in OS was discovered between RO and R1 (univariate), and was nearly verified in the multivariate analysis (p = 0.067). Neoadjuvant chemotherapy did not alter this finding.

In paper II a total of 209 patients (67.4 %) developed recurrence after a median of 4.2 years, and were further stratified between sites; hepatic (n = 90), extrahepatic (n = 59) and both (n = 60). Median TTR and OS were 14 and 45 months, respectively. Synchronous disease, ASA score, increased number and size of metastases were all independently correlated to a reduction in TTR. Hepatic TTR was influenced by synchronous disease, multiple lesions, ASA score and R1 resections, while extrahepatic TTR was correlated to lymph nodes positive of the primary, size and number of metastases. Perioperative chemotherapy increased TTR and OS in the multivariate analysis. Single site recurrence in liver or lungs was most common and with a potential for longevity.

In paper III a total of 20 % (CRR) of the patients with CLM in Norway were resected. In the multivariate analysis the resection rates varied according to age, extrahepatic metastases, disease-free interval and geographical region. In patients diagnosed with CLM, resection doubled the chance for survival. The 3-year survival after resection

was 73.2 %. In the region with the highest CRR, the lowest OS was observed after resection. However the highest OS in the whole cohort of patients with CLM was obtained in this region.

Conclusion:

Positive margins were correlated to adverse outcomes, and were not influenced by preoperative chemotherapy. RMs < 5 mm increased the risk for LR. Number and size of metastases, ASA score, synchronous disease and perioperative chemotherapy influenced time to recurrence. Single-site recurrence had a potential for longevity through repeated resections and multimodal treatment. One in five patients with CLM in Norway are offered resection, depending on geographical regions, age and disease advancements.

List of publications

1. **Angelsen JH**, Horn A, Eide GE, Viste A. Surgery for colorectal liver metastases: the impact of resection margins on recurrence and overall survival. *World journal of surgical oncology* 2014;12(1): 127.

2. **Angelsen JH**, Viste A, IM Løes, Eide GE, Hoem D, Sorbye H, Horn A. Predictive factors for time to recurrence, treatment and post-recurrence survival in patients with initially resected colorectal liver metastases. *World Journal of Surgical Oncology* 2015; 13:328

3. **Angelsen JH,** Horn A, Sorbye H, Eide GE, Loes IM, Viste A: Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway. *The British journal of surgery* 2017 Apr; 104 (5):580-89.

CONTENTS

ABBREVIATIONS

CLM –	Colorectal liver metastases
CRR -	Cumulative resection rates
CRC –	Colorectal cancer
CRN –	Cancer Registry of Norway (Kreftregisteret)
DFI -	Disease-free interval (Time between resection of primary tumour and detection of CLM)
DFS -	Disease-free survival
EGFR-	Endothelial growth factor receptor
LR-	Local recurrence
NPR –	Norwegian Patient Registry (Norsk Pasientregister)
OS -	Overall survival
PRS -	Post-recurrence survival
RCT-	Randomised controlled trials
RM –	Resection margin
TTR -	Time to recurrence

1 INTRODUCTION

1.1 Metastatic colorectal cancer epidemiology

Colorectal cancer (CRC) is one of the most common malignant diseases worldwide. It is estimated approximately 1.2 million new annual incidents, where industrialised and urbanised countries are the largest contributors[1]. In Norway 4265 new incidents of CRC were registered in 2015, ranging as the second most common malignancy in men (after prostatic cancer) and women (after breast cancer)[2]. The last fifty years a significant increase in incidence has been observed, ranging Norway on top compared to other Nordic and European countries.

Figure 11-E: Colon (ICD-10 C18)

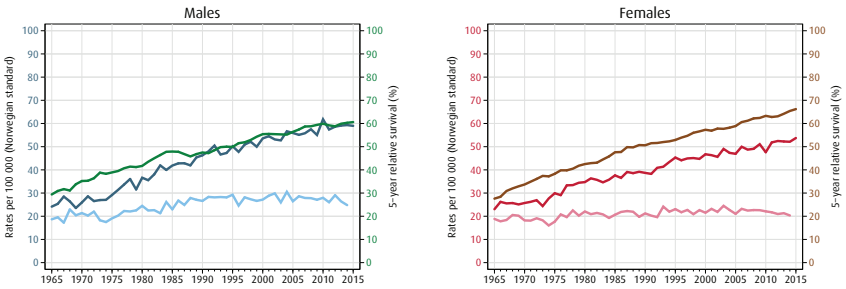


Figure 11-F: Rectum, rectosigmoid (ICD-10 C19–20)

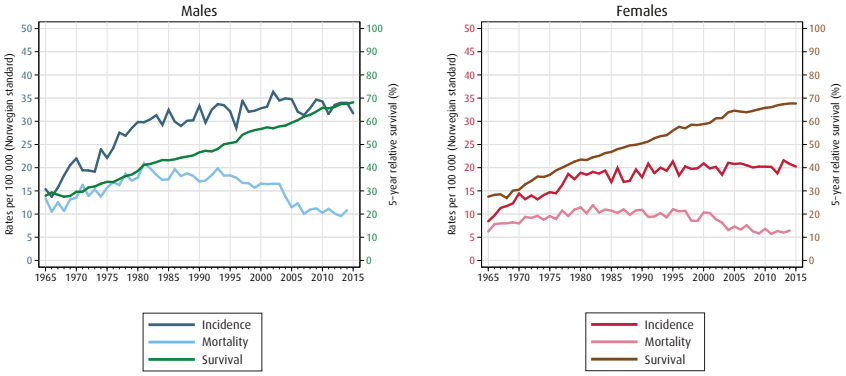


Figure 1: Trends in incidence and mortality rates and 5-year relative survival proportions in Norway[2]. (Cancer in Norway 2015, Norwegian Registry of Cancer)

The rates among women are the highest in Europe. Mainly due to an aging population, the increase will probably continue in the coming years[2].

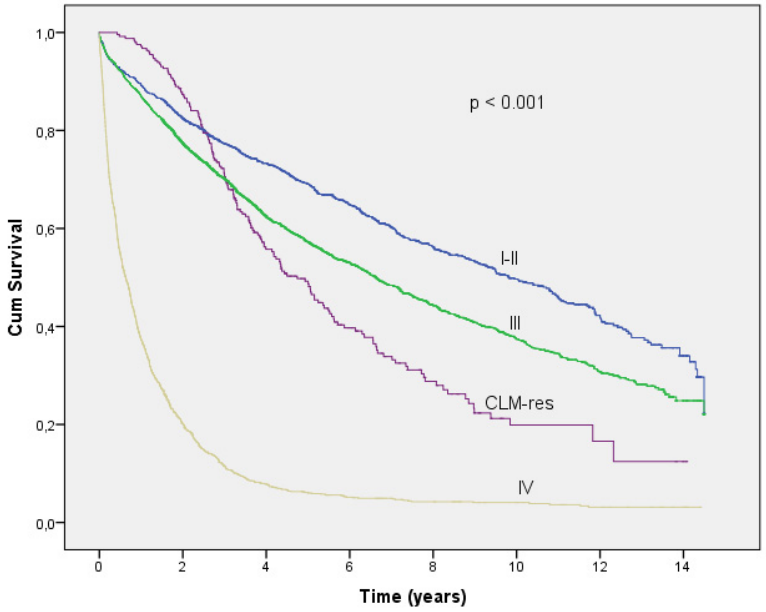


Figure 2: Overall survival in 6372 patients diagnosed with CRC in western Norway (Sogn og Fjordane, Hordaland and Rogaland county) 1998-2012. Five-year (median) OS: Stage I-II: 69.1 % (9.8 years); stage III: 57.3 % (6.3 years); stage IV: 6.0 % (0.6 years); Stage IV-CLM resected: 49.0 % (4.7 years). Unpublished data retrieved from the Cancer Registry of Norway in the catchment area of Haukeland University Hospital.

The relative five-year survival (2011-2015) after CRC in Norway in men is 60.6 % (colon) and 68.2 % (rectum), whereas in women 66.2 % (colon) and 67.7 % (rectum) respectively[2] (Figure 1). The five-year survival rates in CRC are strongly correlated to tumour stage at the time of diagnosis (Figure 2). Generally, approximately 90 % of all cancer related deaths are caused by metastases[3].

Approximately 19-25 % of patients diagnosed with CRC have developed synchronous metastases, while another 20-35 % are estimated to develop metachronous disease during the follow up[4, 5]. This also agrees with unpublished data retrieved from the Norwegian Cancer Registry from the catchment area of Haukeland University Hospital (Sogn og Fjordane, Hordaland and Northern Rogaland counties). In the period 1998-

2010 a total of 20.5 % of 5671 patients developed synchronous metastatic CRC[6]. The occurrence of metachronous dissemination of disease is not well documented. From an abstract based on unpublished data from NPR and NCR (Angelsen, JH et al 2015) 40.0 % of patients registered with CRC (2008-2013) developed metastases, and of these only 26 % had liver metastases (Figure 3)[7]. This is in line with the French population based regional study (Burgundy) where 29 % developed CLM[8].

Prognosis following liver metastases is highly correlated with options for treatment. Patients with unresectable stage IV disease have a grim prognosis (five-year OS 3 %)[9]. In patients only receiving best supportive care, a median OS of 5 months has been reported, and this increased to 11 months when a 5-FU based regimen was administered[10]. Modern optimal oncological palliative therapy yields 20-32 months median survival[11-14]. Surgical intervention (resection or ablation) is the only treatment with a potential for cure with a five-year survival reaching up to 47-58 %[15-17].

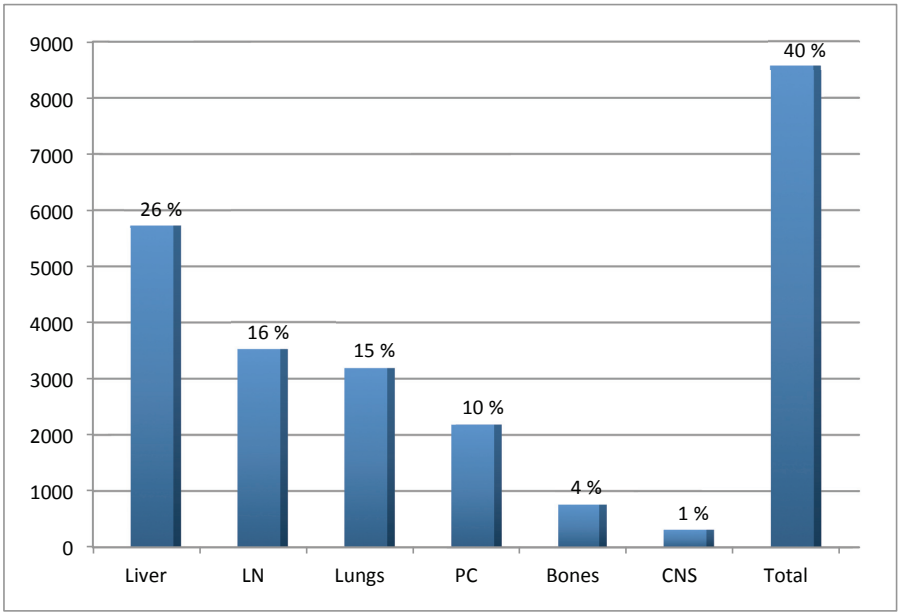


Figure 3: Unpublished data on metastatic pattern from CRC in 21984 patients (2008-2013) in Norway based on synchronized data from NPR and CRN.LN: Lymph nodes, PC: Peritoneal carcinomatosis, CNS: Central nervous system.

1.2 The evolvement of surgical treatment of colorectal liver metastases

1.2.1 Expanding criteria for surgery

Liver surgery has during the last 50 years undergone major development, from the surgeons "no-man`s-land" to a safe and potential curative procedure in patients with malignant disease[18]. The first reported resection of a single metastasis from a rectal cancer was done in 1940[19]. In the 50-60s, liver resection for CLM was tested and reserved for a strictly selected group with solitary small tumours with up to 17 % postoperative mortality[20]. During the 70s and 80s, numerous smaller series were published. In selected patients with small solitary lesions it was reported a 5-year OS of 42% vs. none survivors with multiple CLM[21]. Acceptable results were also published after major resections for large (> 5 cm) solitary lesions with 41 % of patients alive after 3 years (Adson et al, 1980)[22]. In 1984 Cady et al found a cut-off in survival in patients with ≥4 metastases (median OS 13 months with no long time survivors). Consequently they advocated resection when number of metastases was limited (<4), for smaller lesions with observational time 3-6 months in synchronous disease, in order to avoid unnecessary major hepatectomy[23]. Ekberg et al (1986) also recommended resection only in cases with less than four lesions, no extrahepatic disease and a RM of at least 10 mm[24].

A meta-analysis (Hughes et al, 1988) detected that 100 of 859 patients were long time survivors (five-year OS 24 %), some of them with clinical characteristics beyond the previous inclusion criteria[25]. The authors, consisting of leading surgeons and referral institutions in The US and UK, therefore advised an expansion of resectability beyond the former reported contradictions to surgery in selected patients. Despite strict inclusion criteria, a high number of patients experienced recurrence (70-75 %), without any appropriate option for adjuvant chemotherapy[26].

The new millennium was accompanied by further increase in CLM resections with a paradigm shift. While resectability in the old paradigm focused on the characteristics of metastatic disease like tumour size and number, RM >1 cm etc. ("what is

removed"), the new paradigm focused on preserving at least two adjacent well perfused, tumour-free liver segments (20-30% future liver remnant) with adequate bile drainage ("what is left")[27]. The indications for CLM resections have further been expanded to include patients with intended positive RMs[28-30] as well as concomitant extrahepatic disease[29, 31-33].

1.2.2 Introduction of chemotherapy

One of the milestones in the modern treatment of CLM in the 90s was the introduction of chemotherapy in adjunction to liver resection. Bismuth and colleagues presented promising data in 53 initially unresectable patients downstaged with 5-FU, folinic acid and oxaliplatin with a five-year OS of 40 %[34]. In 2004 updated results were published (Adam et al) in a group of 1104 unresectable patients. Following downsizing chemotherapy, a total of 138 (12.5 %) patients were deemed resectable, and underwent surgery with a 5-year survival of 33 %[35]. The Paul-Brousse group was also one of the pioneers in repeated resections and the establishment of multidisciplinary teams customizing individual treatment in each case[36, 37]. Encouraged by the combination of chemotherapy with surgery, patients with initially resectable tumours were also introduced to perioperative treatment in an attempt to gain an increase in OS[38].

1.2.3 Development of novel surgical techniques

Along with expansion of indication for surgery, new techniques evolved. During the late 1980s and the early -90s, right-sided portal vein embolization was introduced as an option to increase the future remnant liver volume prior to extended hemi-hepatectomies, aiming at a higher number of patients for cure[39, 40]. In 2000 the two-stage resection was introduced[41]. Follow-up data revealed completion rates of 65 – 89 % with a postoperative mortality and five-year OS rate of 3 % and 42-51 %, respectively[42-47]. In 2012 the first report on Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) was presented[48]. Ongoing trials will

hopefully clarify many of the questions related to feasibility, morbidity and long-time survival in these two approaches[49]. Further, in 2016 'Enhanced one-stage hepatectomy' was reported as a third method in advanced cases with meticulous preoperative mapping of the liver tumours, with adjacent vessels replacing formal resections with local central resections[50, 51]. Beyond this, liver transplantation has yielded promising results in patients with liver–only unresectable disease[52, 53]. Ongoing trials will hopefully clarify which patients that will be best eligible for inclusion (SECA –II). Radiofrequency ablation -either simultaneous or as sole treatment - has increased the resectability rates and survival in borderline cases, for high-risk comorbid patients or as a palliative treatment[54-57].

Several series have proven the laparoscopic access to be a feasible procedure with comparable results to open surgery as for long-time survival and morbidity, even when major resections are performed[58-60]. In the only RCT performed (Oslo-CoMet RCT), postoperative inflammatory response was found to be lower compared to the open access[61]. Data on postoperative morbidity, pain, discharge and quality of life are waiting to be published[62].

The development of surgical treatment of CLM during the last 50-year period of time could not have been undertaken without the simultaneous advances in diagnostic imaging with contrast enhanced CT, MRI, ultrasonography and PET-scan. Likewise, perioperative safety with development of new surgical equipment, enhanced methods for haemostasis and accompanied by skilled anaesthesiologist has also contributed significantly. However, all these issues are probably beyond the scope of this thesis.

1.3 Preoperative assessments

1.3.1 Stage IV cancer and further stratification

The AJCC Cancer Staging Manual has classified stage IV CRC as spread beyond the regional lymph nodes of the primary tumour irrespective of site and extent of metastatic disease[63]. In the literature there are confusions of a further stratification of stage IV CRC. Further classification of stage IV has been proposed according to resectable vs. unresectable (IVR and IVU) disease. Each of these is further classified into liver only (a), extrahepatic (b) and both (c)[64]. Resectable stage IV cancer has now equal outcome as stage III[65]. With the evolvement of effective chemotherapy and biologic targeted agents, a third group should be included in-between and termed 'potentially resectable' or 'initially unresectable'[65].

Fig 4: Assessments for CLM resections. The challenging area in the decision making for resection is the gray zone in the middle

1.3.2 Defining tecnical resectability and survival benefit

There is a common consensus about technical resectability being defined by macroscopic eradication of tumour with a sufficient preserved future liver remnant (>20-30 %) with adequate vascular supply and bile drainage[66]. Other factors determining the extent of the resection include the patients general condition and eventual impaired liver parenchymal quality due to exposure from chemotherapy or concurrent liver diseases. Before a decicion is made by the MDT board, relevant examination with CT (Thorax/abdomen/liver), MRI liver, eventually PET CT (if suspected extrahepatic disease)[65], CEA measurement and eventual mutation status should be undertaken. Several scoring systems have been developed in order to stratify patient prognosis following surgery:

1. Fong score (Size and number of metastases, disease-free interval (DFI), CEA, RM)[67].

2. Nordlinger score (age, size and number of metastases, DFI, CEA-level, RM, stage primary tumour)[68]

3. Basingstoke Predictive index (>3 CLM, node positive primary, low differentiation primary, extrahepatic disease, tumour >5cm, CEA >60 and R1)[69]

The Nordlinger score stratify patients into three groups according to a scoring system; 0-2, 3-4 and 5-7 with less survival with increasing number. This scoring system has been tested and there were no significant differences between predicted and observed outcome. Neither Fong nor Nordlinger score seems reliable as a prognostic tool in patients receiving preoperative chemotherapy[70]. In 2015 an updated version of the Nordlinger score also included *KRAS* mutation[71]. In 2016 Løes et al expanded the research by exploring intra-individual heterogeneity in metastases as a marker for adverse outcome, where low- (below median) and high-level heterogeneity had a tree-year OS of 18 and 66 %, respectively[72].

However, all these scoring systems are most often less applicable in a clinical setting, and even in patients with the worst score long-time survivors are represented, (i.e. 5-years survival is not zero). Number and size, node positive primaries and extrahepatic disease are all surrogates for genomic factors not yet fully explored and predicting adverse outcome.

1.3.3 Common clinical scenarios

1.3.3.1 Solitary metacronous CLM

Patients presenting with resectable solitary metastases with some elapsed time from resection of the primary, represents probably the easiest decision making for the MDT-board. If the tumour is accessible for laparoscopy, this should be the preferred method[58]. The indication for perioperative chemotherapy in such cases is controversial[73]. With small sized solitary lesions upfront surgery is probably an adequate option[73]. Perioperative chemotherapy could be administered in cases with elevated CEA >5.0[74].

1.3.3.2 Initially unresectable CLM

Defining resectability might be challenging. Different scenarios are often encountered, ranging from patients with large hepatic tumour load only, to those with concurrent extrahepatic disease in need of response to chemotherapy before assessed as beneficial for surgery. The conversion rates from unresectable to resectable are highly correlated to the response and tumour volume reduction following optimal chemotherapy (Figure 6)[75]. There is a mixture of reports also including patients with extrahepatic metastases, which preclude the interpretation of the true meaning of downsizing[75]. Please also see 1.4.1 Downsizing chemotherapy.

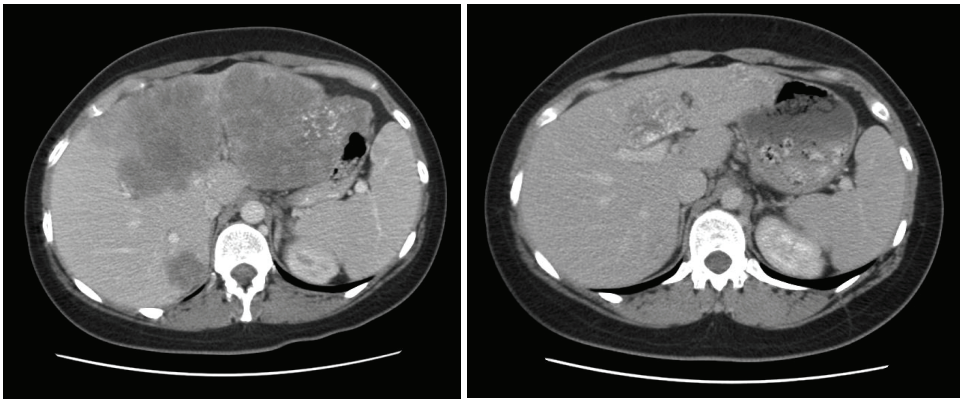


Figure 5. Patient with initially unresectable CLM downsized with chemotherapy (Irinotecan) and Bevacizumab. Left: baseline, right: after six cycles. Later on, a left hemihepatectomy and right-sided wedge resections were performed.

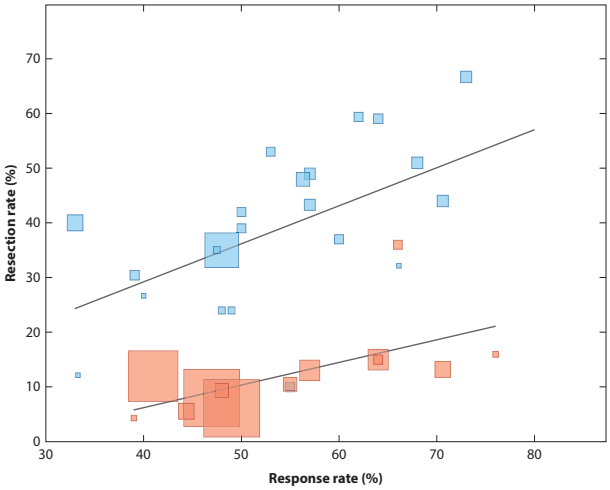


Figure 2

Rates of secondary liver resection following systemic chemotherapy. The size of each data point reflects the number of patients included in each study. Blue squares denote series that had clearly defined criteria of irresectable disease. These show a highly significant correlation between response rate and secondary resection rate ($R^2 = 0.62$, $p = 0.003$) with high rates of conversion to resectability. Red squares represent series without clearly defined criteria for irresectability, which also show a significant correlation between response rate and secondary resection rate ($R^2 = 0.71$, $p = 0.004$). For studies with clearly defined criteria for resectability, rates of secondary resection were much higher for similar rates of radiological response ($p = 0.006$) (46).

Figure 6: Correlation between radiologic response and secondary resection following chemotherapy for initial unresectable CLM (Jones et al)[75]. The figure is copied with permission from the author.

1.3.3.3 Synchronous CLM

There are divergent definitions of 'synchronous' in the literature; detection of metastases at the same time or before primary tumour[76], 3 months[57], 4[77] or 6 months after detection of the primary[78]. Several surgical options in patients with resectable CLM and primary tumour in situ exist: 1) Staged resection with primary tumour resection first, 2) Liver-first approach, 3) Simultaneous colorectal and liver surgery. So far, no RCTs have demonstrated the optimal choice of treatment in synchronous disease. In an international expert panel the majority advised perioperative chemotherapy as a standard to all patients with synchronous CLM[76].

1.3.3.3.1 Primary tumour resection first (bowel-first)

In cases with symptomatic, locally advanced primary tumour (i.e. occlusion or tumour bleeding) and minor liver deposits, primary surgery needs priority before liver resection. Upfront primary surgery, re-stage 2-3 months later, and CLM resection if stable disease was previously the traditional approach in synchronous disease. Interval re-evaluation avoided unnecessary resection in 2/3 of the patients (Lambert et al, 2000)[79]. In the study by Gall et al (2014), 53 patients with synchronous liver metastases from rectal cancer were treated with neoadjuvant chemotherapy (and radiation if indicated), primary resection and finally liver surgery with promising overall 5-year survival of 39 %[80].

1.3.3.3.2 Liver-first approach

Since the metastases rather than the primary tumour determine survival, upfront chemotherapy followed by liver resection and completion with resection of the primary has been applied to accomplish tumour eradication. This reverse strategy has been considered as optimal in patients with asymptomatic primary tumour and advanced CLM[81]. Patients aimed for liver-first treatment present more advanced disease, but no significant differences in OS or disease-free survival (DFS) compared with 'bowel-first' when performing a propensity score-match of preoperative tumour

load (Welsh et al, 2016)[82]. Completion rate following the 'liver-first' strategy is reported as 73-85 % with a 3-year survival of 41-79 %[83-86]. In cases with locally advanced rectal cancer in need of preoperative radiotherapy, the following treatment algorithm is an option in our department: Chemotherapy (depending on primary resectability of CLM) – short course radiotherapy (5 x 5 Gy), followed by liver resection, and finally rectal surgery.

1.3.3.3.3 Simultaneous resections

In patients with resectable synchronous CLM, it is tempting to perform simultaneous resections (primary tumour and CLM). In several studies this approach has proved to be as safe as staged resections and with shorter total hospital stay[87]. However, complex major hepatectomies combined with primary surgery should be avoided due to the risk for adverse complications[76, 88]. Major liver resections (≥3 segments) was the only predictor for severe complications (Clavien-Dindo >3) in 43 patients undergoing simultaneous resections at Haukeland University Hospital[89]. In several meta-analyses no significant differences could be obtained in long-time results between sequential and simultaneous treatment[90, 91].

The complexity and heterogeneity of patients with synchronous CLM accompanied with the absence of RCTs on optimal treatment entails individual patient approach in the MDT-board. None of the three approaches (bowel-first, liver-first or simultaneous) has proven superiority according to complications, early mortality, DFS and OS[92]. However, each modality has its own advantage in certain circumstances depending on i.e. advancement of local tumour and hepatic lesions. The HPB units should therefore master all three options.

1.3.4 CLM with extrahepatic disease

During the last 10-20 years, an expansion of inclusion criteria has accepted surgical intervention for CLM also in patients with resectable extrahepatic disease[32]. Most

patients will experience recurrence, but due to the increased focus on oncological therapies, OS seems acceptable in selected cases[32]. The most common sites of extrahepatic metastases are the lungs, lymph nodes in the hepatic pedicle or distant and in the peritoneum. Metastases to the brain or the bones are less common. From a serial of 840 patients Adam et al (2011) showed that extrahepatic disease predicted lower OS, especially in extrahepatic metastases other than lungs[33]. A recent meta-analysis by Hadden et al (2016) found a five-year OS of 26 %, and a median OS 42 months with concomitant lung metastases following CLM resection and 17 % and 29 months (five-year and median OS) with peritoneal metastases[32]. In patients with lymph node metastases the median and five-year survival was 25 months and 15 %, respectively[32]. However, location of lymph node involvement affects survival (Adam et al, 2008); as lymph nodes in the hepatic pedicle reveals a far better prognosis (5-year OS 25 %) compared to metastases to the coeliac trunk or distant para-aortic nodes (no 5-year survivors)[93]. In cases with CLM and limited peritoneal carcinomatosis, hepatic resection with simultaneous cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is a feasible option[94]. Patients with CLM and extrahepatic metastases have a decreased OS compared to liver-only metastases, and when an increased frequency of resections is performed in cases with advanced disease, the survival rates will probably converge with the expected results from palliative chemotherapy alone.

1.4 Chemotherapy

When chemotherapy is administered it is either given as perioperative, in initial resectable cases, or as downsizing regimens when initially deemed unresectable. In a downsizing approach, patients are offered the most efficient, yet tolerable regimen in an attempt to reach resectability. In the perioperative setting, patients are offered oxaliplatin- based chemotherapy in conjunction with a planned resection.

1.4.1 Downsizing chemotherapy

Resectability rates after chemotherapy in unresectable CLM varies widely (6-60 %), most probably due to divergent definitions, local chemotherapy algorithms and study design[95]. There is a significant correlation between response rates to chemotherapy and the following resection rates (Figure 6). This supports to choose the most aggressive regimen tolerable to reach resectability and thus potential long time survival[95]. The Norwegian Gastro Intestinal Cancer Group (NGICG) recommends first line treatment with double-agent chemotherapy (5-Fu with oxaliplatin or irinotecan) optionally combined with EGFR inhibitors in *KRAS* wild type[96]. Triple agent regimen (5-Fu+ oxaliplatin + irinotecan) is an option for fit patients with *BRAF* or *RAS* mutations. Multiplicity of different chemotherapeutics and targeted drugs increase the response rates (up to 70 %) but also the toxicity[97-101].

1.4.2 Perioperative chemotherapy

At Haukeland University Hospital perioperative chemotherapy is administered as six cycles of Nordic FLOX[102] before surgery followed by 6 cycles after surgery. Perioperative chemotherapy is offered to oxaliplatin-naive patients < 76 years of age with ECOG performance status 0-1 and CEA > 5.0[38, 74, 103]. Other perioperative regimens have not yielded advantages in outcome[104-106]. Complete response and

vanishing CLM is a challenge with several treatment options (resection vs. surveillance)[107-109].

Perioperative chemotherapy combined with complete resection intends to eradicate micrometastases and increase the chance for durable survival[110]. Other advantages not clearly tested in RCTs include detection of chemoresponsiveness as a predictor for further treatment and as a prognostic factor, especially in synchronous disease[107, 111, 112]. Likewise, tumour shrinkage with intended increased complete resection will preserve more parenchyma in a liver sparing approach[113]. However, perioperative chemotherapy is a double-edged sword. Chemotherapy might induce liver injury and increase the risk for postoperative morbidity[38, 114].

1.5 General considerations on resection margins

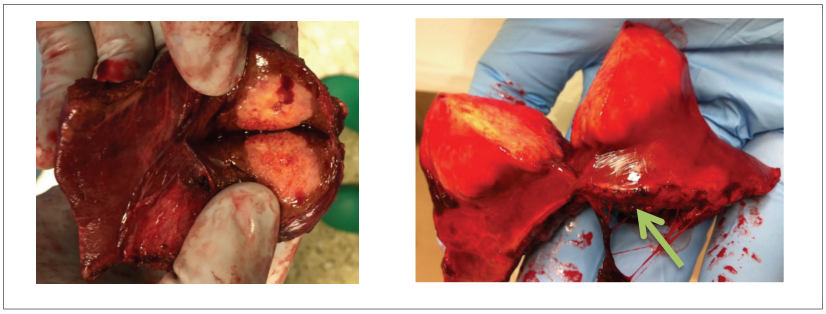


Figure 7: Successful resections of CLM with macroscopic free margins with an irregular transection zone (arrow). Photo: JH Angelsen

During the years with increased inclusion for surgery, and with a shift from anatomical to parenchyma preserving wedge resections, the RMs have probably narrowed. The R1 rates might have increased as well. To study if these changes have influenced the outcome is therefore vital. Defining the extent of the RMs could be a challenging manoeuvre for the pathologist. Several factors are related to these uncertainties:

1. Irregular transection surface due to various instruments (i.e. CUSA, ultrasonic aspirator, Harmonic scalpel, Kelly clamp technique or electro cautery devices)

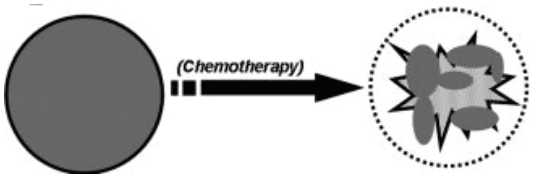


Figure 8: Model of chemotherapy response in CLM. The untreated lesion (left) has a sharply defined surface. In cases with tumour response to chemotherapy (right),an irregular surface appears with tentacles of viable tumor and centrally fibrosis that replacing former tumour necrosis. The figure is copied with permission from the author[115].

2. Chemotherapy response in CLM induces apoptosis and fibrosis with centripetally tumour shrinkage, leading to an irregular tumour surface as detailed in figure 8 (Ng et al)[115]. In borderline resectable metastases, the transection line might pass through the previous tumour area (Fig 9). The use of ultrasound dissection increases the width of crushed parenchyma as well[116]

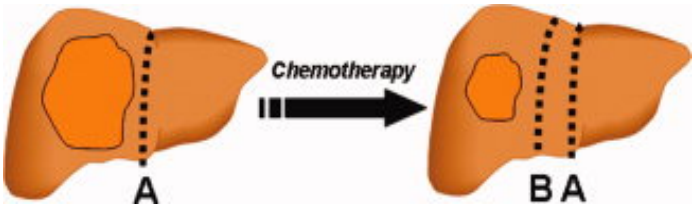


Figure 9: Left: Intended transection line (A). Right: Response on chemotherapy, the new transection line (B) passes through previous tumour area. The figure is copied with permission from the author[115].

3. During transection, an estimated loss of tissue in the resected area is estimated to be 5-8 mm[117]. Therefore, a positive margin does not automatically mean tumour left in the remnant liver.

4. Hypoxic zones induce the growth of remnant micro metastases[118, 119]. This is assumed to be a mechanism in RFA treatment but could also be the same in the remnant tumour border following surgery.

5. Satellite lesions surrounding the main tumour are observed in variable degree in tissue samples surrounding the main tumour at a maximum range of 4 mm[120-122]. The lesions are most common within 2 mm from the main tumour with decreasing frequency beyond this.

1.6 General considerations on recurrence

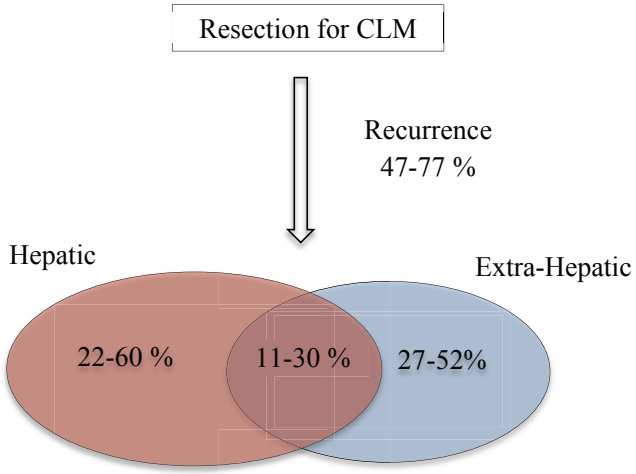


Figure 10: Patterns of recurrence after resection for CLM[123-129].

Since most patients will experience post-resection relapse, detailed knowledge of the recurrence pattern is vital. Following this, understanding which baseline characteristics predisposing for recurrence is of major interest. Especially interesting is the study of the post-recurrence prognosis in different sites that might guide the treatment more efficiently. Based on clinical experience, patients with lung metastases seems to progress slowly, it is therefore interesting to study if this site of relapse should have some implications for a CLM re-resection.

The liver is the most common site of metastases of colorectal origin (~90 %) due to the portal flow, whereas lung metastasis without liver involvement is less frequent (<10 %)[130]. A higher incidence of isolated lung metastases has been observed from rectal cancer compared to colon primaries, most probably due to direct haematogenous spread through inferior rectal veins bypassing the portal circulation[130]. Isolated metastases downstream of the lungs (i.e. bone or brain metastases) without any further liver or lung involvement are extremely rare[131]. Tumour cells might also spread through the lymphatic system and enter local or distant lymph nodes. Detection of

lymph node metastases is an adverse prognostic marker in CRC, and it is not known whether the occurrence of distant organ metastases is a sequential process (lymphatic – haematogenous) or two independent routes[132]. After CLM resection, the liver is the most common single site of recurrence followed by lung recurrence (Figure 10).

Several mechanisms might induce the recurrence in different sites. Undetected intrahepatic residual tumour cells deposited at an earlier point might progress after resection. Several studies have documented elevated regenerative growth factors (i.e. hepatocyte growth factor) that stimulate proliferation of remnant tumour cells following resection[133]. Experimental studies in mice have proven that the extent of recurrence and the speed of tumour growth both hepatic and extra-hepatic is highly correlated to the extent of resection[134]. During the recent years an increasing knowledge has evolved on cancer stem cells that exhibit features of colonizing distant sites through evolvement of adapting sub-clones to the target environment[135].

1.7 Resectability from a national perspective

The number of patients with CLM offered resection has increased dramatically during the last 15-20 years. At Haukeland University Hospital there has been a five-fold increase in annual resections in this period (Figure 11). The reasons for this expansion are mainly due to more liberal inclusion criteria for surgery, altered referral practice, establishment of multi-disciplinary boards, multi-modal treatment and improvements in surgical skills and facilities.

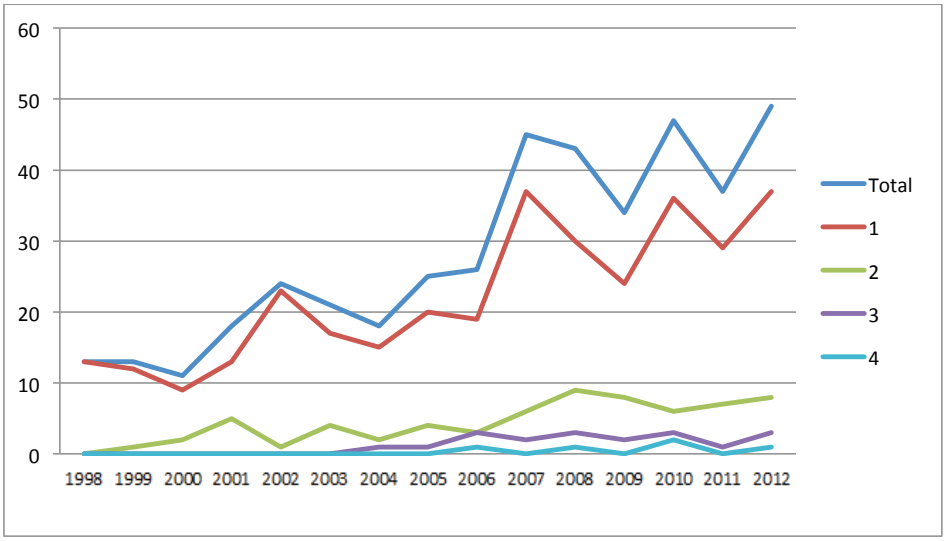


Figure 11. Expansion of liver resections at Haukeland University Hospital (1998-2012). Total number of resections (1-4) per patient.

Several questions arise following these advances: 1) Are the quality of the treatment acceptable, including peri-and postoperative morbidity/mortality and long-time results? 2) Are there any regional differences that should be stressed? 3) Do the technical resectability and operability criteria differ among the HPB-units? 3) Does the expansion of resection rates yield an increase in survival for the total amount of patients with CLM?

Significant geographical and institutional variations both in referral practice and selection for surgery have been documented (England, USA and the Netherlands)[136-140]. Rapid changes and new modalities in oncosurgical treatment might induce intermediate differences across regions and countries. To obtain knowledge of the quality and equality of treatment for patients with CLM from a macro perspective, national surveys should be performed based on available population based registry data. Some of these questions are aimed to be answered in this thesis.

As hundreds of single centre series have proven survival benefits following CLM surgery, no future RCT is ever intended to be undertaken[140]. On the other hand, most of these publications are based on highly selected patients in specialised centres biasing the results when it comes to an overall insight of outcome following such treatment. National surveys are therefore warranted. After introduction of CLM surgery in a larger scale around 20 years ago, the resection rates might now be assumed to be in a nearly steady state. The Norwegian model with four health trusts with regional centres containing MDT-boards and oncosurgical expertise ease the opportunity to make population based studies. Likewise, with authority directed national registries like the CRN and NPR, with obligation to record incidence and treatment of cancer, yield additional benefit for national research.

2 AIMS OF STUDY

2.1 Paper I

The purpose of this paper was to study LR, TTR and OS according to the RM status in patients undergoing surgery for CLM. We further wanted to analyse if chemotherapy altered the RMs impact on outcome.

2.2 Paper II

The purpose was to analyse the sites of recurrence after liver resections for CLM and the factors influencing TTR in different sites. Further we aimed to study the treatment of post-resection recurrence and the impact on survival according to site of relapse.

2.3 Paper III:

By merging two national registries, we wanted to explore the proportion of patients with CLM in Norway undergoing resection. Following this, we further aimed to study factors affecting the resection rates i.e. geographic regions, age, and locations of the primary tumour.

3 PATIENTS AND METHODS

3.1 Permissions and ethical considerations

In 2008 the establishment of a local database was undertaken at Haukeland University Hospital with consecutive series of patients treated with surgery for colorectal liver metastases from 1998 onwards. In March 2009, an application was submitted to the Regional Committee for Medical and Health Research Ethics (REK-Vest)[141]. The study was approved as a quality assurance study in May 2009 (project number 098.09). This decision was appealed and after a new assessment the project was finally approved in 2010 as a scientific study and became under law by "Ethical Guidelines and the Norwegian Research Ethics Act (Helseforsikringsloven) from 01.07.2009 (project number 2010/2514). As for the retrospective registration part of the study from 1998-2008 an exemption of informed consent was accepted, and from 2009 in the prospective registration a written permission from the patients was obtained.

In February 2015 an application was submitted to REK-Vest for establishing a database from patients registered in NPR and CRN with CRC. The project entitled "Forløpsanalyse av pasienter med spredning fra tykk- og endetarmskreft i Norge" (project number 2015/324) was accepted in April 2015. Exemption to informed consent was accepted whereas permission for storage of data in the hospital`s research server was obtained as well.

3.2 Establishment of a local registry

Using SPSS version 21, a database containing the following parameters was developed: Patient ID, gender, date of birth, ASA score, location of primary tumour, date of resection (primary), TNM stage, date of detection of CLM, number and location of CLM, preoperative chemotherapy, indication (downsizing or

perioperative), , number of cycles, response (RECIST)[142], CEA, date of CLM resection, type of resection, simultaneous resection of the primary, time of operation, postoperative complications (Clavien-Dindo)[143], date of discharge, RMs, number and size of largest CLM, tumour differentiation, date of recurrence, location of recurrence (LR, intrahepatic other sites, extrahepatic (lung, abdominal, brain, bones etc.), date of death, status at last date of follow-up (healthy, alive with recurrence, death caused by recurrence and death by other causes).
The registry was updated annually according to recurrence and vital status. RMs <1 mm were defined as positive (R1)[16]. Data were retrieved from the patients' medical records. The patients were prospectively followed up with CT-scan and vital status until November 2012.

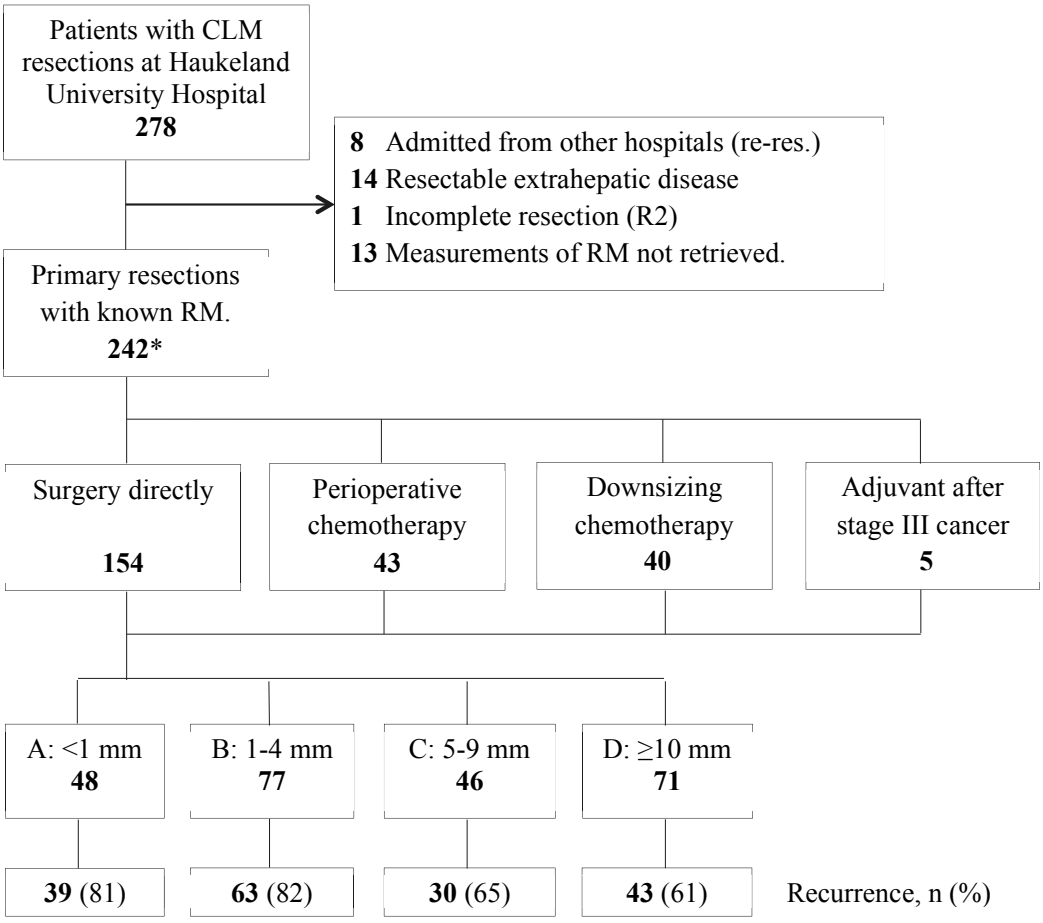
3.3 Data extraction from Norwegian patient registry and the Cancer Registry of Norway (2011-2013).

Diagnosis and treatment registered in NPR were classified using International Classification of Diseases (ICD-10) and the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical/Medical Procedures (NCSP/NCMP), respectively. Patients with the diagnoses of C18-20 (CRC) and C78.7 (liver metastases) were extracted from NPR and synchronized with patient with CRC in CRN from the same period of time. Patients in NPR without any code in CRN were excluded along with cases of appendiceal cancers (C18.1). Patients registered in CRN (C18-20) with a defined benign diagnosis registered in NPR were included as well. Information about vital status (alive or deceased) was synchronized with the Norwegian National Registry (Folkeregisteret). Patients registered with diagnoses C18-20 and C78.7 without any registrations of any code for liver resection were assumed to be unresectable.

3.4 Study population

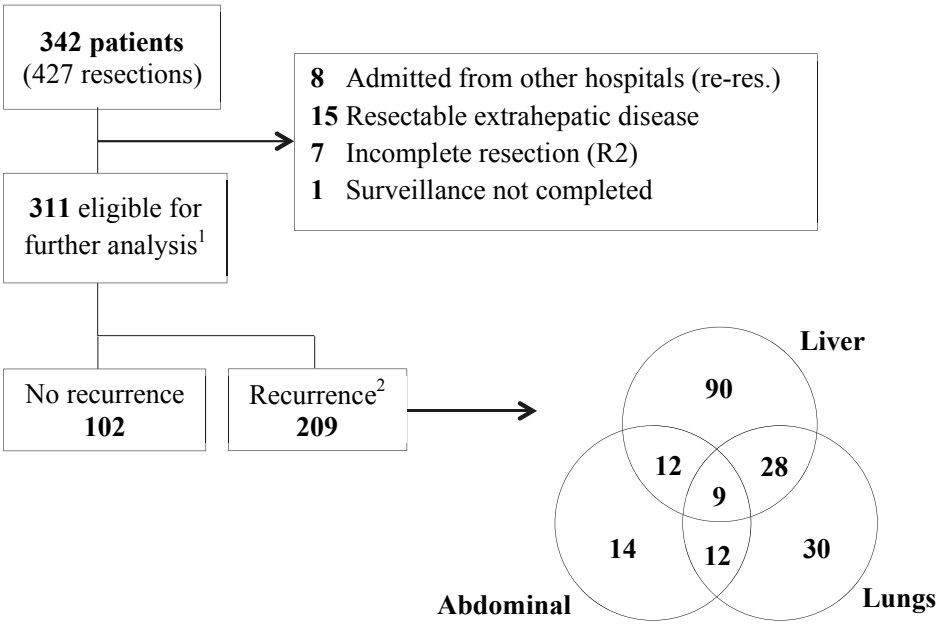
Haukeland University hospital is the only HPB-centre in the catchment area of approximately 0.7 million people living in Sogn- og Fjordane, Hordaland and Northern Rogaland county. The data are therefore assumed to be population based.

Figure 12: Study algorithm in paper I (1998-2010):



**Patients with known R-status (R0 vs. R1): n = 253, unknown R0/R1: n = 2.*

Figure 13: Study algorithm in paper II (1998-2012):



Chemotherapy:

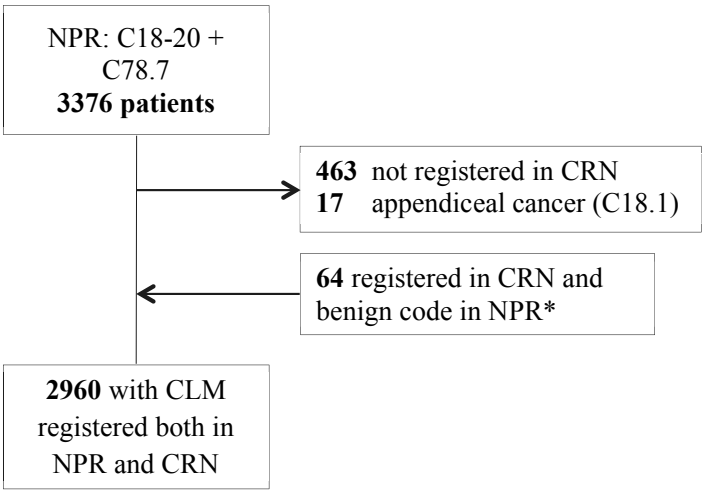
[1]*Upfront surgery: n = 199; Perioperative chemotherapy: n = 59; Downsizing chemotherapy: n = 46; Adjuvant chemotherapy after stage III CC: n = 7.*

[2]**Recurrence (other combinations):**

cerebral only, n = 1; liver/bones, n = 2; liver/cerebral, n=1; lungs/cerebral, n = 2; liver/lungs/cerebral, n = 1; liver/abdominal/bones, n = 2; liver/lungs/bones, n=4; liver/ovary n = 1.

Median follow-up 4.2 years.

Figure 14: Study algorithm in paper III (2011-2013):



**benign diagnosis: Diverticulitis (K57.3), benign colorectal neoplasm (D12.6-8), neoplasm of uncertain behaviour (D37) and inflammatory bowel disease (K50-52).*

3.5 Statistical analysis

The following statistical analyses have been performed in paper I-III:

1. *t* test: Normally distributed continuous variables
2. Mann–Whitney *U* test: Non-normally distributed continuous variables
3. The Kruskal-Wallis one-way analysis of variance test: Analyzing more than two non-normally distributed samples
4. The exact chi-square ($\chi 2$) test: Categorical variables
5. Multinomial logistic regression: Analyzing the probabilities of the different possible outcomes of a categorically distributed dependent variable.
6. Cox proportional regression[144]: Multivariate analysis

7. Multiple fractional polynomial regression[145]: Multivariate analysis evaluating non-linear phenomena in continuous variables (such as RMs).
8. Kaplan-Meier method[146]: Survival analysis of incomplete observations, tested for significance with the log-rank test[147].
9. Adjusted Kaplan-Meier method (Competing risk assessments): In the calculation of resection rates some obstacles concerning competing risk analyses appeared due to multiple outcomes (resection, death or alive without resection). In a traditional Kaplan Meier analysis, events not included in the analysis, will be censored. According to Lau and Andersen et al, a competing event (i.e. death) may impede the event of interest (i.e resection) from occurring[148, 149]. Some extensions in the survival analysis should therefore be undertaken by retaining censored subjects (death) in the risk set. Resection rates were then finally obtained using 1-(Kaplan-Meier$_{(adjusted)}$).

Overall survival (OS): time from diagnosis or resection to death irrespective of cause

Time to recurrence (TTR): Time interval between resection and a relapse[150]. TTR and not DFS was preferred in the assessment of recurrence pattern, due to treatment-related and non-cancer-related deaths as endpoints in the latter definition[150]. These patients were censored in the estimation of TTR.

Local recurrence (LR): defined by CT scan as a new appearing lesion in contact with the previous resection surface.

4 SUMMARY OF RESULTS

4.1 Paper I

Patients undergoing R1-resections presented more advanced disease compared to R0-resections. They were further grouped according to margin width; A: R1, <1 mm (n = 48, 19%), B: 1 to 4 mm (n = 77), C: 5 to 9 mm (n = 46) and D: ≥10 mm (n = 71)[157]. Overall recurrence was detected in 175 (72.3 %) patients, of these LR was found in 40 (16.5 %) patients. LR without recurrence in any other sites was detected in 14 cases (5.8 %). LR occurred more frequently with RMs < 5 mm compared with 'no recurrence' (multinomic logistic regression analysis). Postoperative chemotherapy was administered more frequently after R1 resections.

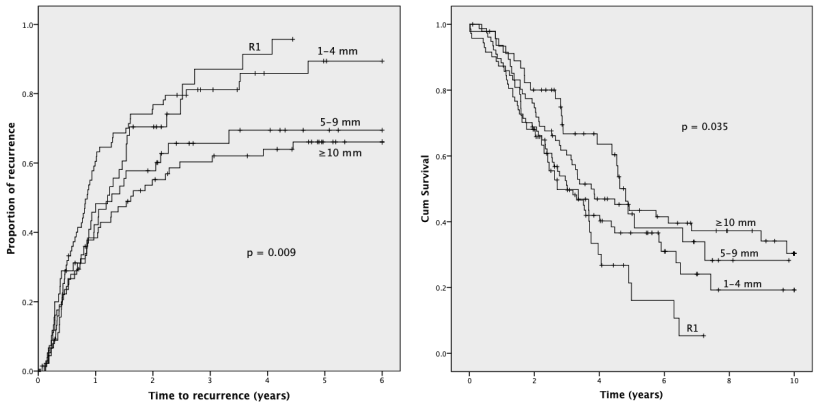


Figure 15: TTR (left) and OS (right) according to RMs in 242 patients with resection for CLM. Figure left: R1 (A) vs. R0 (B-D): p = 0.127, < 5 mm (A and B) vs. ≥ 5 mm (C and D): p = 0.001, < 10 mm (A-C) vs. ≥ 10 mm (D): p = 0.020. Figure right: R1 (A) vs. R0 (B-D): p = 0.011, < 5 mm (A and B) vs. ≥ 5 mm (C and D): p = 0.008, < 10 mm (A-C) vs. ≥ 10 mm (D): p = 0.239

TTR increased significantly with increasing extent of RM. There was an insignificant difference in 5-year TTR between R0 and R1, whereas TTR was significantly longer for RM ≥ 5 mm vs. < 5 mm. No additional benefits in TTR were obtained with RMs above 10 mm. Fifty patients underwent a second liver resection due to intrahepatic recurrence, and 20 of those had recurrence in the RM (LR). Five-year OS in R0 and R1 was 42.5% and 16.1%, respectively ($P = 0.011$). In the multivariate analysis, R1-resections predicted adverse outcome (p = 0.067) without any alterations when preoperative chemotherapy was administered.

4.2 Paper II

Among 311 eligible patients, 209 (67.4 %) developed post-resection recurrence at a median of 4.2 years (hepatic: 90; extra-hepatic: 59 and both: 60). Median TTR and OS were 14 and 45 months, respectively. TTR was stratified according to overall, hepatic and extrahepatic recurrence. In a multivariate analysis synchronous disease, ASA score, multiplicity and size of lesions were related to a reduced TTR, whereas perioperative chemotherapy extended TTR and OS. Hepatic TTR was influenced by synchronous disease, multiplicity, ASA score and R1 resections, while extrahepatic TTR was correlated to positive lymph nodes from the primary tumour, size and number of CLM. Patients undergoing perioperative chemotherapy had a better outcome compared to surgery alone (5-year OS: 57 vs. 37 %, p = 0.024), also verified in the multivariate analysis. In those completing the perioperative regimen five-year TTR and OS were 43 and 62 %, respectively (Figure 16).

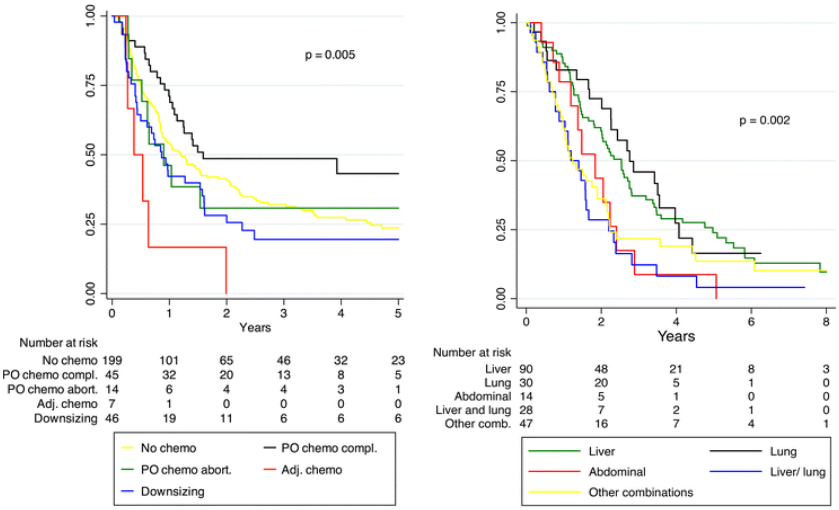


Figure 16 (left) TTR according to different chemotherapy regimens. Figure 17 (right): Post recurrence survival according to sites of recurrence.

Single-site recurrence was most commonly found (135 of 209, 64.5 %). Median post recurrence survival (PRS) was 24 months, and varied according to site of relapse: Lungs (32.3), liver (30.5), abdominal (22.0), liver + lungs (14.3) and miscellaneous (14.8), p = 0.002 (figure 17).

4.3 Paper III

Analyses of data from 2011-2013 revealed that 20 % of patients with registered CLM in Norway underwent a liver resection. The multivariate analysis discovered that cumulative resection rates were associated with age, region, DFI and extrahepatic disease ($p<0.05$). Median OS after detection of CLM was 11 months. OS following diagnosis of CLM was influenced by liver resection, age, region, tumour site, DFI and extrahepatic metastases (all $p<0.05$). One-, three-, and four-year post-resection survival was 94, 72 and 55 %, respectively. Regional affiliation was the only factor

correlated to post-resection OS in the multivariate analysis (p = 0.037). OS was not affected by age. 30-day postoperative mortality rate was 0.9 % (5 patients).

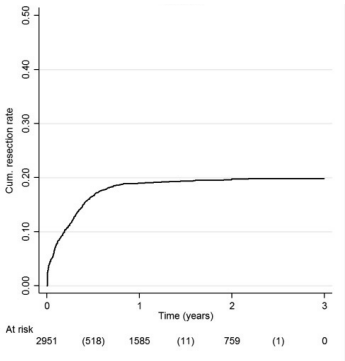


Figure 18: Cumulative resection rates following detection of CLM in Norway (2011-2013).

5 DISCUSSION

5.1 Resection margins

5.1.1 R0 vs. R1

In the 80- and 90-ies the "1-cm rule" was advocated in several papers[24, 151, 152]. The results from paper I demonstrate the necessity of clear margins as an attempt to gain an optimal outcome that is in line with the majority of recent published papers[16, 67, 69, 153-158]. Positive margins also tended to predict an adverse outcome in the multivariate analysis ($p = 0.067$) with no alteration following administration of preoperative chemotherapy ($p = 0.081$). Macroscopic incomplete tumour eradication (R2) is in general not recommended in CLM surgery[159]. However, an adverse outcome of microscopic positive tumour margin (R1) remains questionable, especially in the era of efficient chemotherapy. Several reports have presented equivalent outcome (OS and DFS) between R0 and R1 resections along with neoadjuvant chemotherapy, in contrast to the current study[28, 30, 159, 160]. Other authors argue that in laparoscopic resection positive margins do not seem to affect outcome[161, 162]. This is explained with a more frequent use of thermal destructive devices compared to open surgery leaving a coagulation zone eliminating eventual remnant tumour cells. Further, resection of lesions close to intrahepatic vessels (vascular R1) the OS is comparable to R0-resections[51]. In paper II, we discovered that preoperative chemotherapy responders with an R1 resection experienced a shorter TTR compared to R0 resections, but this finding (R0 vs R1) was not evident in patients with stable disease. Tumour shrinkage of the metastases in response to chemotherapy might lead to remnant islets of tumour cells, increasing the probability for recurrence following narrow or positive margins[115].

5.1.2 Resection margins as surrogate for other biologic factors

RMs might also be a surrogate variable representing other adverse biologic factors. Instead of acting like an independent predictor of adverse outcome, RM might also be

a consequence of the extent of tumour load. Several reports have demonstrated that R1 was associated with increased risk of recurrence and an adverse biologic baseline like elevated CEA (>200), multiplicity, bilobar lesions, and *RAS* mutation[16, 163, 164]. The same findings were observed in our study, where R1 was associated with extensive tumour load compared to R0[157]. Several studies have in multivariate analyses failed to demonstrate R1 as a genuine predictor for survival[16, 163]. The adverse outcome following R1 resections might be derived from aggressive tumour biology rather than from remnant cancer cells[159]. This is supported by a study showing that re-resection in patients with intraoperative detected positive margins did not yield improved outcome[165].

5.1.3 The extent of negative surgical margins

There have been conflicting results regarding the optimal width of the free margins. DNA- and histopathologic analysis of tissue samples surrounding the main tumour have revealed satellite lesions at a maximum range of 2-4 mm, which justify a rational basis for the extent of the RMs[120-122]. Paper I documented an increased risk of local and global recurrence accompanied narrow RMs (<5 mm). This cut-off value was also associated with reduced OS in the KM analysis, although not verified in the multivariate analysis. Other reports have documented 2, 3 or 5 mm as sufficient margins for an optimal outcome[121, 166, 167]. In a study by Are et al (2007) the outcome in patients with >1 cm margin was independently better compared with <1 cm and R1, although the authors argued that possible subcentimeter resections should not exclude patients for surgery[163]. Several other papers have proved the outcome to be unaffected by the extent of free margins[16, 153, 154, 168-171]. In the search of the correlation between RMs and survival we applied multiple fractional polynomial regression without detecting any non-linear relationships (i.e. logarithmic correlation) [157]. One recent study from Memorial Sloan Kettering Cancer Centre (2015) including 2368 patients detected an independent correlation between RMs and OS (Figure 19)[172]. An

increasing margin width, also including submillimetre resection had a prolonged OS compared to R1.

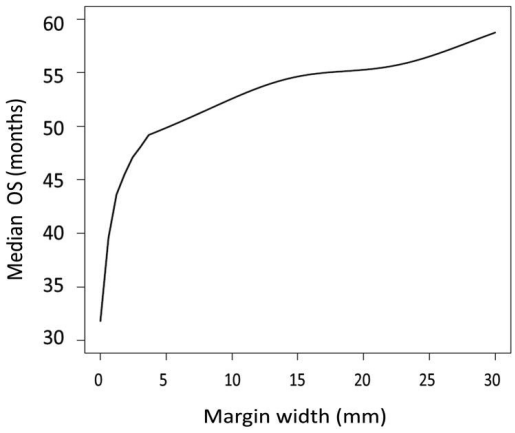


Figure 19: Median survival following resection for CLM according to RMs in 2368 patients at Memorial Sloan Kettering Cancer Center, NY[172]. The figure is copied with permission from the author.

5.2 Patterns of recurrence

5.2.1 Location of recurrence

In paper II we found that number of metastases was the only independent factor affecting overall, hepatic and extrahepatic TTR [125]. Several other reports emphasise the prognostic importance of multiplicity[128, 129]. Despite this, patients with >8 metastases can achieve long time survival provided by response to chemotherapy[173].

Hepatic recurrence was in the current study influenced by multiplicity, R1 resections and synchronous disease. This is presumably caused by undetected remnant deposits of micrometastases. The higher number of resected lesions or positive margins, the more likely it is that micrometastases are left behind. Several of these factors have

been confirmed by other studies, in addition to history of RFA and colon primary tumour[17, 127].

From the literature it is shown that rectal cancer primary indicates increased risk for extrahepatic recurrence (especially lungs), whereas hepatic recurrence was more often seen in colon primary[174-176]. In paper II none of these associations were discovered. Mutative disease promotes extrahepatic relapse including lungs (*KRAS*)[177, 178] and peritoneal or distant lymph nodes (*BRAF*)[179].

5.2.2 Chemotherapy and recurrence

The present study revealed a prolonged TTR and OS in patients receiving perioperative chemotherapy compared to surgery alone. This finding was confirmed in the multivariate analysis. Further increase in survival was found in those patients completing the intended perioperative regimen. In 2008 the EORTC intergroup RCT trial 40983 was published (Nordlinger et al) proving an increase in progression-free survival[38] with oxaliplatin based perioperative chemotherapy (FOLFOX 4) + surgery vs surgery alone in patients with initially resectable CLM. However, follow up data could not reveal any significant benefit in OS (Nordlinger et al, 2013)[103]. Nevertheless, patients with CEA > 5.0 had a benefit from perioperative chemotherapy (Sørbye et al, 2012)[74]. Several randomised trials have investigated outcome after adjuvant treatment, and detected only marginal benefits of 5-Fu based regimens[180-182], although one retrospective study reported an independent favourable outcome[183].
The encouraging results found following perioperative chemotherapy in our retrospective cohort of highly selected patients, should be interpreted with cautions. This study is not an "intention to treat analysis" with randomised patients, and selection biases might exist. On the other hand, patients receiving chemotherapy (both perioperative and downsizing) presented more advanced disease with a higher number of metastases and a larger frequency of synchronous metastases compared with the surgery alone group.

Patients receiving downsizing chemotherapy had higher tumour load compared to those undergoing upfront resection, but their TTR was not significantly adverse (p = 0.155). This is also outlined in other papers where patients converted to resection, inherited nearly equal and acceptable outcome compared with initially resectable patients[35].

5.2.3 Survival according to patterns of recurrence

Survival was found to be highly correlated to number of relapsing sites. Patients with liver or lung recurrence had a median PRS of 30 and 33 months, respectively, superior to all other sites or combinations. Only nine patients with lung metastases were resected (paper II). Despite this, median survival reached nearly three years in this group. Slow-growing unresectable lung metastases should therefore not be a contradiction for liver resection in selected patients with concomitant CLM[31]. Patients with solely hepatic recurrence offered re-resection had a PRS of 50 months, compared with 20 months when chemotherapy was administered alone. A similar OS was observed when comparing the first and the second resection (five-year OS: 39 % vs. 37 %). This is also consistent with several other reports[184-186].

5.3 Resection rates

Paper III is the first national unselected cohort study published with synchronous and metachronous CLM undergoing resection. Several regional based studies (France, Germany and the Netherlands) have reported similar rates (10-35 %)[187-189]. One Swedish and a Dutch national study have both published a resection rate of 18 % in patients with synchronous CLM[190, 191]. However, none of these presented data on metachronous disease.

Variations in resection rates were seen according to different ages where 40-59 years had the highest frequency followed by 60-74, <40 years, 75-79 and lowest in patients

>80 years. An advanced metastatic tumour load might cause a relative low resection rate in younger patients (< 40 years) [192]. The CRR among octogenarians was low (6 %). No significant difference in post-resection survival was observed in this group compared to the rest of the cohort. Other reports have shown the same results, with tumour advancement and not age being predictors for outcome in elderly patients[193, 194]. In the Nordic registry study (Sørbye et al 2013), the improvements in survival during the last decades was primarily seen in younger patients, probably due to some reluctance in advocating advanced and novel treatment in elderly patients[4]. Based on these findings, a higher proportion of fit octogenarians with CLM could probably have benefited from a resection.

Rectal cancer primary was a borderline significant factor for increased resection rates ($p = 0.056$), with significant better OS ($p < 0.001$) in patients diagnosed with CLM. Data from the CRN has previous proven that implementation of national strategies for rectal cancer have yielded improvements in outcome[195].

Some geographical variations were also observed among the four regional health trusts in Norway. Between South-East (reference) and the West trust a difference in resection rates was detected (highest in the West), although a lower post-resection OS was found in the West compared with South-East. Finally, the OS for all patients with CLM in the West were significant higher compared with the reference. One could therefore speculate if resection rates and post-resection OS are inversely related. Variations in referral practice from local hospitals to HPB units as well as different inclusion criteria for resection exist[136-138].

The difference in CRR varied between the four health trusts (19-24 %), although we do not assume this difference to be of clinical importance. In the Dutch registry, the inter-hospital variations in resection rates were more prominent (14-34 %)[139]. The same variation was evident in the British study (Morris et al. 2015) based on percentage of hepatectomies according to surgery for CRC (range 0.7-6.8 %)[140]. Variation in preferences in referral from local hospitals to the HPB units might also influence the resection rates. Krell et al. (2015) discovered differences in referral

pattern among oncologists in local hospitals to their HPB-centres[138]. The geographic regions in paper III were further based on patient's residency and not the location of the treating HPB-unit. Several patients are referred from other regions to Rikshospitalet (South East) for a second opinion. An eventual resection will be credited their home region in the analyses described in paper III.

In the data from NPR/CRN, no information of morbidity was retrievable. The 30-days mortality rate was low (< 1 %).

5.4 Limitations and biases

5.4.1 Pre and postoperative evaluations

In the two first papers we reported a fairly high number of patients with recurrence (paper I and II: 72 % and 67 % with a median follow up of 4.7 and 4.2 years, respectively). One important bias is that preoperative contrasted enhanced MRI was implemented as a standard examination after the end of the study, thus underestimating the extent of liver lesions. There is an international consensus about preoperative MRI should be performed in addition to CT scan in these patients[196]. Likewise, routinely measurement of preoperative CEA was not undertaken the first couple of years in the study.

In paper III it should be noted that there were no retrievable data of preoperative diagnostic modalities[197]. Further, there were no data on preoperative staging, like number of liver metastases, size, bilobar etc. The TNM stage was retrieved (paper III) from CRN and the Norwegian Colorectal Cancer Registry, but according to missing values this predictor had to be removed from further statistical analyses.

5.4.2 Epidemiological challenges and biases

In paper III available surveillance data like post-resection recurrence and treatment options in surgery-naive patients were not available. Such data are difficult to obtain in large registry studies. Further, observational studies encompasses a variety of biases with selection and registration of cases (i.e. diagnosis and treatment codes)[198]. On the other hand, due to financial reimbursement of registration of diagnosis and procedures in Norwegian public hospitals, the completeness of these data is assumed to be high.

The completeness of the CRN is reported to be about 98.8 %[199]. Due to the lack of complete follow-up data, synchronizing with NPR was undertaken. Some inconsistencies in incidence and tumour site have been detected between the two registries[200]. This bias was handled by including only patients with simultaneous registration in both CRN and NPR.

Postoperative surveillance following primary resection of CRC varies in Norway according to tumour location. Patients with primaries in the colon are most often followed by the general practitioner, whereas patients with rectal cancer are followed by specialists in the outpatient clinics. Follow-up in older patients are probably also less frequent than in younger patients. This might induce a "lead-time bias" where the detection of CLM varies between different groups of patients (i.e. age and location of the primary tumour). Lead time is the interval between the detection of a disease through screening or follow-up and its clinical presentation[201]. In paper III, this problem could have been handled by calculating survival from the detection of the primary tumour and not from the date of detection of the liver metastases. On the other hand, this kind of calculation would have induced an "immeasurable time bias"[202] where the patients developing CLM were "immortal" during the period from the resection of the primary to the detection of disseminated disease.

6 CONCLUSIONS

- Resection margins (R0 vs. R1) seems to predict outcome after resection for CLM. LR occurred more frequent in RMs <5 mm.
- Preoperative chemotherapy did not alter the need of free margins.
- Time to recurrence was influenced by the extent of free margins. RMs > 5 mm reduced the risk significantly with no additional benefit exceeding 10 mm.
- Recurrence after CLM surgery occurred in liver (43 %), extrahepatic (28 %) and both (29 %). Single site recurrence was most common (65 %).
- Independent predictors for overall TTR were synchronous disease, ASA score, multiplicity and size of lesions (all adverse) and perioperative chemotherapy (favourable).
- Hepatic TTR was influenced by synchronous disease, multiplicity, ASA score and R1 resections.
- Lymph node positive primary tumour, size and number of CLM were all associated with extrahepatic recurrence.
- Single-site recurrence had the best OS (lungs and liver).
- A total of 20 % of patients diagnosed with CLM in Norway (2011-2013) underwent resection.
- Age, region, DFI and extrahepatic disease were independently associated with resection.
- Resection halved the risk for an unfavourable outcome in patients with CLM.
- Regional affiliation was the only predictor associated with survival following CLM resection.

7 FUTURE PERSPECTIVES

The “holy grale” for the treating surgeon is an accurate prediction of outcome in patients with CLM taking into account several clinicopathological and genetic factors. So far, most staging systems focus on clinical and morphological aspects, but the bases for these findings are probably highly correlated to intra- and extra-cellular signals and genetic tumour behaviour. So far, neither the tumour genome with a variety of mutations nor its correlation to post-resection outcome is fully explored. Future research might therefore guide us to a better selection of patients with advanced disease not benefiting from major surgery.

During the last fifty years, a revolution has taken place in liver surgery. From a careful beginning and till now, the limits have been pushed, in some cases to the extreme. Long-time survival has increased with a simultaneous decrease in perioperative morbidity and mortality. However, the recurrence rates remain at the same high level. In the future a wider discussion of health related quality of life needs to be emphasised in conjunction with expected post-resection survival. Most probably the next step will not be more radical surgery, but evolvement of novel personalised and precise oncological therapy.

Finally, in a country with a large number of local hospitals with small catchment areas, some variations in treatment and referral practice of patients with metastatic CRC might exist. With further development of novel multimodal treatment options, the need for a continuing development of coordination of treatment algorithms is therefore required within each health trust.

“If I have seen further, it is by standing on the shoulders of giants”

Letter from Isaac Newton to fellow scientist Robert Hooke 5th of February 1676

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RESEARCH Open Access

Surgery for colorectal liver metastases: the impact of resection margins on recurrence and overall survival

Jon-Helge Angelsen[1,2*], Arild Horn[1], Geir Egil Eide[3,4] and Asgaut Viste[1,2]

Abstract

Background: Several reports have presented conflicting results regarding the association between resection margins (RMs) and outcome after surgery for colorectal liver metastases (CLM), especially in the era of modern chemotherapy. The purpose of this study was to evaluate the impact of RMs on overall survival (OS), time to recurrence (TTR) and local recurrence (LR) status, particularly for patients treated with preoperative chemotherapy.

Methods: A combined retrospective (1998 to 2008) and prospective (2008 to 2010) cohort study of consecutive patients with CLM without extrahepatic disease treated with primary resection at a medium volume centre.

Results: A total of 253 patients with known R status and 242 patients with defined margin width were included in the study. Patients were stratified according to margin width; A: R1, <1 mm (n = 48, 19%), B: 1 to 4 mm (n = 77), C: 5 to 9 mm (n = 46) and D: ≥10 mm (n = 71). Median time to recurrence was 12.8 months, and after five years 21.5% had no recurrence. LR (inclusive combined recurrence in other hepatic sites or extrahepatic) occurred in 40 (16.5%) cases, most frequently seen with RMs below 5 mm. Five-year OS was 42.5% in R0 and 16.1% in R1 resections ($P = 0.011$). Patients were also stratified according to preoperative chemotherapy (n = 88), and the difference in five-year OS between R0 (45.1%) and R1 (14.7%) was maintained ($P = 0.037$). By multiple Cox regression analysis R1 resections tended to an adverse outcome ($P = 0.067$), also when adjusting for preoperative chemotherapy ($P = 0.081$).

Conclusions: R1 resections for colorectal liver metastases predict adverse outcome. RMs below 5 mm increased the risk for LR and shortened the time to recurrence. Preoperative chemotherapy did not alter an adverse outcome in R1 vs. R0 patients.

Keywords: Colorectal liver metastases, Resection margin, Overall survival, Local recurrence, Time to recurrence, Preoperative chemotherapy

Background

Resection for colorectal liver metastases (CLM) has been well established during the last three decades, with a reported five-year survival of up to 64%, depending on selection criteria and preoperative risk factors [1-3]. In all intended curative cancer surgery a complete removal of the tumor is of major importance. During the 1980s and 1990s authors recommended 'the 1 cm rule' [4-7] that probably resulted in rejection of many patients from CLM surgery. Several reports from the last decade have shown that resection margins (RMs) are less important as long as R0 status is obtained [1,8-11]. In other reports 2 mm [12] and 5 mm [13] have been suggested as sufficient. Finally, some authors have even justified intended R1 resection following great progress in pre- and post-operative chemotherapy treatment due to an acceptable long-term outcome [14-16].

In an advanced stage IV cancer disease like CLM most patients are beyond curative treatment. In patients with resectable metastases, the surgical approach and the RMs are some of the few non-biological factors influenced by the surgeon. The purpose of this manuscript was therefore to analyse in detail the local recurrence (LR) pattern,

* Correspondence: jhangelsen@gmail.com
[1]Department of Acute and Digestive Surgery, Haukeland University Hospital, N-5021 Bergen, Norway
[2]Department of Clinical Medicine, University of Bergen, N-5020 Bergen, Norway
Full list of author information is available at the end of the article

time to recurrence (TTR) and overall survival (OS) with respect to the R1/R0 status and the magnitude of free RMs in patients with primary resection for CLM. We also wanted to explore whether chemotherapy altered the RMs impact on survival.

Methods

Haukeland University Hospital is a tertiary referral centre located in Western Norway, and serves a population of one million. This study is a patient-based cohort with a consecutive series of patients with CLM treated at a single institution (1998 to 2010). Data from the period 1998 to 2008 were retrospectively recorded, and prospectively collected from 2008 to 2010. Data were retrieved from the patients' medical records. All patients were prospectively followed up with respect to survival and other characteristics until November 2012. Variables analysed were TNM stage of primary tumour, time in months between resection of primary tumor and diagnosis of liver metastases (disease-free interval), number and size of metastases, chemotherapy (number of cycles, response and indication), date of liver resection, complications and in-hospital mortality, recurrence and death (perioperative, cancer-related and other causes). RM status was obtained from the microscopic measurements in the histological reports. RMs <1 mm were defined as positive (R1), in accordance with Pawlik *et al.* [9].

Preoperative evaluation

The selection criteria for surgery in our centre included a sufficient remaining tumour-free liver volume (30%) with adequate blood perfusion and bile drainage, and absence of: a) non-resectable extrahepatic metastases, and/or b) no disseminated disease as evaluated preoperatively. Patients with extrahepatic disease and R2 resections were excluded from the current study. Preoperative investigations included computed tomography (CT) scan of the chest and abdomen/pelvis, and tumour marker analysis (CEA: carcinoembryonal antigen). In cases with an inconclusive CT scan, magnetic resonance imaging (MRI) of the liver, contrast-enhanced ultrasound and 18 F-fluorodeoxyglucose ^{18}(FDG)-positron emission tomography (PET)/CT scan were performed. Each patient was discussed in a multidisciplinary team meeting with surgeons, oncologists and radiologists.

Chemotherapy

Preoperative chemotherapy (n = 88) was given in a perioperative setting (n = 43) or as a downstaging procedure (n = 40) in patients with initially deemed unresectable disease. Five patients developed CLM during adjuvant treatment with chemotherapy after resection of stage III colon cancer. We evaluated the outcome of chemotherapy by the Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1 [17]. The size of the metastases was measured on CT scan by dedicated radiologists. All patients in the perioperative group were offered the FOLFOX regimen (fluorouracil, leucovorin and oxaliplatin) with an intended six cycles before and after surgery. They were evaluated with CT scan after three and six cycles. The indication for perioperative chemotherapy has changed during the period. A total of 17 patients were enrolled in the European Organisation for Research and Treatment of Cancer (EORTC) multicentre study 40983 and randomised for surgery alone (n = 7), or surgery with perioperative chemotherapy (n = 10) in the period 2001 to 2004 [18]. After that, patients <76 years with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and no previous treatment with oxaliplatin had been offered perioperative chemotherapy. In the downstaging group, patients were treated with several different chemotherapy regimens as listed in Table 1. First-line treatment with the Nordic FLOX or FLIRI regimen was most commonly used, optionally in combination with EGFR (endothelial growth factor receptor) inhibitors or angiogenesis inhibitors.

Surgical procedures

Surgical techniques included subcostal incision, intraoperative ultrasonography, occasionally repeated inflow control (the Pringle manoeuvre), and transection using Ultracision, Kelly clamp and Cavitron Ultrasonic Surgical Aspirator (CUSA). Throughout the period we have intended to achieve a parenchyma-sparing approach, with wedge resections whenever possible. Formal resections (hemihepatectomies or lobectomies) have been reserved for metastases placed centrally or near the hepatic veins. To increase intended complete tumour eradication, intraoperative radiofrequency ablation, and portal vein ligations/embolization with two-stage resections have been performed. Simultaneous colorectal cancer surgery has been reserved for healthy patients with colon cancer and less advanced CLM. Further details are listed in Table 1.

Surveillance

Follow-up after surgery included CT scan of the chest, abdomen and pelvis every three months for the first two years, and thereafter every six months for the next three years. Serum level of CEA tumour marker was obtained every third month. We defined LR by CT scan as a new lesion in contact with the previous resection surface. The resected area was easily detected with CT due to the wide use of metallic clips during the transection. The data were based on the first detection of recurrence. Data of recurrence were not available in four patients. Patterns of recurrence were stratified according to LR, hepatic recurrence (without LR) and extrahepatic recurrence. LR included patients with a) LR only, b) LR and

Table 1 Clinical characteristics and administration of chemotherapy in 253 patients with primary resection for colorectal liver metastases

Variable, *statistics*	Estimate
Age in years, *median (range)*	66.1 (22.8, 89.2)
Gender *male/female ratio*	133/120
Synchronous metastases[a], *n (%)*	115 (45.5)
Disease-free interval[b] in months, *median (range)*	4 (-14,131)
Resections, *n*	253
Hemihepatectomy/lobectomy, *n (%)*	117 (46.2)
Wedge/segment resections, *n (%)*	136 (53.8)
Simultaneous radiofrequency ablation, *n (%)*	12 (4.7)
Two-stage resections, *n (%)*	3 (1.2)
Simultaneous colorectal cancer surgery, *n (%)*	14 (5.5)
Extent of resection margin in mm, *median (range)*	4 (0-50)
Number of metastases, *median (range)*	2 (1, 12)
Metastases diameter in cm, *median (range)*	3.0 (0.2,15.0)
Bilobar metastases, *n (%)*	94 (37.2)
Number of resections/patient (1/2/3/4/5)	203/36/11/2/1
In-hospital mortality, *n (%)*	4 (1.6)
Follow-up survivors in years, *median (range)*	4.7 (1.9-12.9)
Chemotherapy preoperatively, *n (%)*	88 (34.8)
Downstaging, *n (%)*	40 (15.8)
Perioperative[c], *n (%)*	43 (17.0)
Adjuvant after colon surgery, *n (%)*	5 (2.0)
Type of chemotherapy	
FOLFOX[d], *n (%)*	71 (81.6)
FOLFIRI[e]/+bevacizumab, *n (%)*	8/3 (9.1/3.4)
FOLFIRI + cetuximab, *n (%)*	1 (1.1)
FLV[f], *n (%)*	3 (3.4)
Other combinations, *n (%)*	5 (5.7)
Outcome of chemotherapy[g] (RECIST)	
Partial response, *n (%)*	52 (59.1)
Stable disease, *n (%)*	32 (36.4)
Progression, *n (%)*	2 (2.3)
Unknown, *n (%)*	2 (2.3)
Number of cycles	
≤3	11 (12.5)
4-6	40 (45.4)
7-12	27 (30.7)
>12	7 (8.0)
Unknown	3 (3.4)
Chemotherapy adjuvant, *n (%)*	44 (17.4)
After neoadjuvant, *n (%)*	30 (11.9)
After downstaging, *n (%)*	7 (2.8)
Without preoperative chemotherapy, *n (%)*	7 (2.8)

[a]Synchronous metastases: detected <1 month after surgery of primary colorectal tumor; [b]disease-free interval: time from resection of primary colorectal tumor to detection of hepatic metastases; [c]all patients were offered the FOLFOX regimen; [d]FOLFOX (oxaliplatin, 5-fluorouracil, leukovorin); [e]FOLFIRI (irinotecan, 5-fluorouracil, leukovorin); [f]FLV (5-fluorouracil, leukovorin); [g]RECIST-criteria measured by computed tomography scan.

relapse in other sites of the liver and c) LR with concomitant new extrahepatic lesions. During the follow-up, thirteen patients died from causes other than colorectal cancer, and six from treatment-related causes. These patients were also included in the analysis of OS, according to the definition stated by Punt *et al.* [19].

Statistical analysis

Variables with possible impact on OS like RM, age, size, number of metastases, bilobar distribution, disease-free interval and TNM stage of primary tumour were analysed with univariate and multivariate survival methods. The exact chi-square (χ^2) test was used for categorical variables, the t test for normally distributed variables, and the Mann–Whitney U (MWU) test for non-normally distributed continuous variables. The Kruskal-Wallis one-way analysis of variance test was used to compare more than two non-normally distributed samples. Multinomial logistic regression was used to evaluate LR in relation to RMs. Survival was estimated by the Kaplan-Meier method [20] and tested for significance with the log-rank test [21]. Multivariate analysis was performed as Cox proportional regression [22]. Continuous predictors such as RMs were also modelled using multiple fractional polynomial regressions [23]. A P value ≤0.05 was considered significant. OS was defined as time from resection to death irrespective of cause, and TTR was defined as the interval between resection and the detection of a local or distant relapse [19]. All analyses were performed using SPSS Statistics version 19 (IBM Corp., Armonk, NY, USA) and Stata 12 statistical software (StataCorp, College Station, TX, USA). We decided to use TTR rather than disease-free survival as a parameter in assessing recurrence patterns, since the latter has treatment-related and non-cancer-related deaths as endpoints, which could be misleading according to the definition by Punt *et al.* [19].

Ethics

The Regional Committee of Ethics of Western Norway Health Authority approved the study, with an exemption to the requirement for obtaining informed consent from

patients included in the retrospective part (1998 to 2008). In the prospective part (2008 to 2010) patients were enrolled through written consent.

Results

In total, 278 patients underwent 353 resections in the 13-year period. Among these, 270 patients underwent a primary (first) liver resection. Eight patients were admitted from other hospitals for re-resections. Fourteen patients (5.2%) with primary resectable extrahepatic metastases (thirteen pulmonary and one pelvic) were not included in the current study. One patient could not complete the second procedure of a two-stage liver resection due to progression of disease. The R0/R1 status was not obtained in two patients, whereas the exact resection margin (in millimetres) could not be defined in eleven cases.

Finally, a total of 253 patients with known R status and 242 patients with a defined margin width were eligible for further analysis. Patients were further sub-grouped according to margin width obtained from the histological report; A: R1, <1 mm (n = 48), B: 1 to 4 mm (n = 77), C: 5 to 9 mm (n = 46) and D: ≥10 mm (n = 71). Clinical and pathological features are listed in Table 1. Positive microscopic margins (R1) were found in 48 cases (19.0%).

Patient and tumour demographics

R1 patients had more advanced disease compared to R0 according to bilobar locations ($P = 0.007$, χ^2-test) and number of metastases ($P = 0.099$, MWU test). There was no significant difference between R0 and R1 patients in the TNM status of primary tumour in colon or rectum, American Society of Anesthesiologists (ASA) score, size of the metastases and the use of preoperative chemotherapy. Postoperative chemotherapy was administered more frequently in R1 patients (n = 12 of 48, 25.0%) compared to R0 (n = 31 of 205, 15.1%), $P = 0.016$, χ^2-test. In the chemotherapy group, there was no difference in number of R1 resections between patients with partial response or stable disease using the RECIST criteria ($P = 0.575$, χ^2-test). In the perioperative and the down-staging group a total of thirty (69.8%) and seven (17.5%) patients, respectively, underwent postoperative chemotherapy ($P < 0.0001$, χ^2-test).

Patterns of recurrence

Global recurrent disease occurred in n = 175 (72.3%) patients, whereas involvement of the resection surface was found in 40 cases (16.5%). Further details are listed in Table 2. We found a lower global recurrence in the groups C and D compared to A and B. The risk for recurrence according to RMs (A to D) was assessed with a multinomial logistic regression, as detailed in Table 3. The odds ratios for LR were significantly higher in groups A and B relative to group D. RMs did not seem to impact hepatic recurrence, whereas extrahepatic recurrence was more frequent compared to no recurrence with RMs <5 mm (0.005). A total of 21.5% of the patients were recurrence-free after five years. TTR increased significantly ($P = 0.009$) with the increasing extent of the RMs (Figure 1a), but this difference was repealed when we omitted those patients (n = 40) with all kinds of LR ($P = 0.097$). We also detected a non-significant difference in five-year TTR between R0 (24.5%) and R1 (0%, $P = 0.127$). No additional benefit for TTR was seen with RMs beyond 10 mm, where the groups C and D were nearly equal in outcome (Figure 1a).

A total of 50 of 253 (19.8%) patients underwent a second operation for resectable recurrence. Twenty (40.0%) of these were due to LR after the first resection. In 27 cases

Table 2 Global recurrence and local recurrence (LR) following n = 242 primary resections for colorectal liver metastases according to resection margins (RMs)

	Resection margins				
Recurrence	**A (R1) n (%)**	**B (1-4 mm) n (%)**	**C (5-9 mm) n (%)**	**D (≥10 mm) n (%)**	**All n (%)**
LR only	7 (14.6)	3 (3.9)	3 (6.5)	1 (1.3)	14 (5.8)
LR and hepatic	3 (6.3)	3 (3.9)	3 (6.5)	1 (1.3)	10 (4.1)
LR and extrahepatic	6 (12.5)	10 (13.0)	0 (0.0)	0 (0.0)	16 (6.6)
LR (total)[1]	16 (33.3)	16 (20.7)	6 (13.0)	2 (2.8)	40 (16.5)
Hepatic only	8 (16.7)	15 (19.5)	7 (15.2)	22 (31.0)	52 (21.5)
Extrahepatic	13 (27.1)	31 (40.3)	17 (37.0)	18 (25.4)	79 (32.6)
Unknown	2 (4.2)	1 (1.3)	0 (0.0)	1 (1.3)	4 (1.7)
Global[2]	39 (81.3)	63 (81.8)	30 (65.2)	43 (60.5)	175 (72.3)
No recurrence	9 (18.8)	14 (18.2)	16 (34.8)	28 (39.4)	67 (27.7)
Total	48 (100)	77 (100)	46 (100)	71 (100)	242 (100)

Extrahepatic recurrence: recurrence outside the liver with or without hepatic involvement. Statistics: $P = 0.0003$ (χ^2 two-sided exact test) when all groups were included.
[1]LR (total): the sum of 'LR only', 'LR and hepatic' and 'LR and extrahepatic'.
[2]Global recurrence: the sum of 'LR (total)', 'hepatic only', 'extrahepatic', and 'unknown recurrence'.

Table 3 Results from multinomial logistic regression of recurrence according to resection margins (RMs) in n = 242 patients with known recurrence status after primary resection for colorectal liver metastases

Recurrence†	RM	OR	95% CI	*P* value
Local	R1, <1 mm	24.89	(4.77, 129.69)	0.0001
(n = 40)	1-4 mm	16.00	(3,22, 79.56)	0.001
	5-9 mm	5.25	(0.95, 29.15)	0.058
	≥10 mm	1.00	Reference	
Hepatic only	R1, <1 mm	1.13	(0.38, 3.42)	0.827
(n = 52)	1-4 mm	1.36	(0.55, 3.41)	0.508
	5-9 mm	0.56	(0.20, 1.59)	0.274
	≥10 mm	1.00	Reference	
Extrahepatic*	R1, <1 mm	2.25	(0.80, 6.33)	0.126
(n = 79)	1-4 mm	3.44	(1.45, 8.18)	0.005
	5-9 mm	1.36	(0.67, 4.08)	0.276
	≥10 mm	1.00	Reference	

†Reference category is 'no recurrence' (n = 67). Unknown recurrence pattern in n = 4 patients. *Extrahepatic: recurrence outside the liver with or without hepatic involvement. RM, resection margins; OR, odds ratio; CI, confidence interval.

(54.0%), recurrence was found in other sites of the liver whereas only three patients (6.0%) had combined intra- and extrahepatic relapses. In patients with LR only, 11 of 14 (78.6%) patients were resected. Of the 48 patients having a primary R1 resection, 15 (31.3%) underwent a second operative procedure.

Overall survival

Five- and ten-year OS survival rates were 38.7% and 23.0%, respectively, whereas median OS was 45.0 months. Five-year OS of R0 vs. R1 was 42.5% and 16.1%, ($P = 0.011$, Figure 1b), whereas median OS in R0 and R1 were 48.1 and 32.4 months, respectively. By sub-grouping according to margin width (A to D), an increased OS was seen in the univariate analysis ($P = 0.035$, see Figure 1b). However, there was no extra benefit when the RMs exceeded 10 mm (group C vs. D). Patients were also stratified according to preoperative chemotherapy (n = 88), and the difference in five-year OS between R0 and R1 was maintained ($P = 0.037$). In the perioperative group (n = 43), a non-significant difference ($P = 0.502$) in five-year OS was seen between R1 (34.3%) and R0 (54.2%). In the downstaging group (n = 40), the five-year OS was 40.2% for the R0 cases vs. none survivors in the R1 group ($P = 0.017$). Patients with initially unresectable metastases had more extensive disease evaluated as the average number of metastases (3.6) compared to the perioperative (2.5) and the surgery alone group (2.3), using Kruskal-Wallis test ($P = 0.002$). Positive RMs also predicted a borderline significant adverse outcome in the Cox proportional hazards

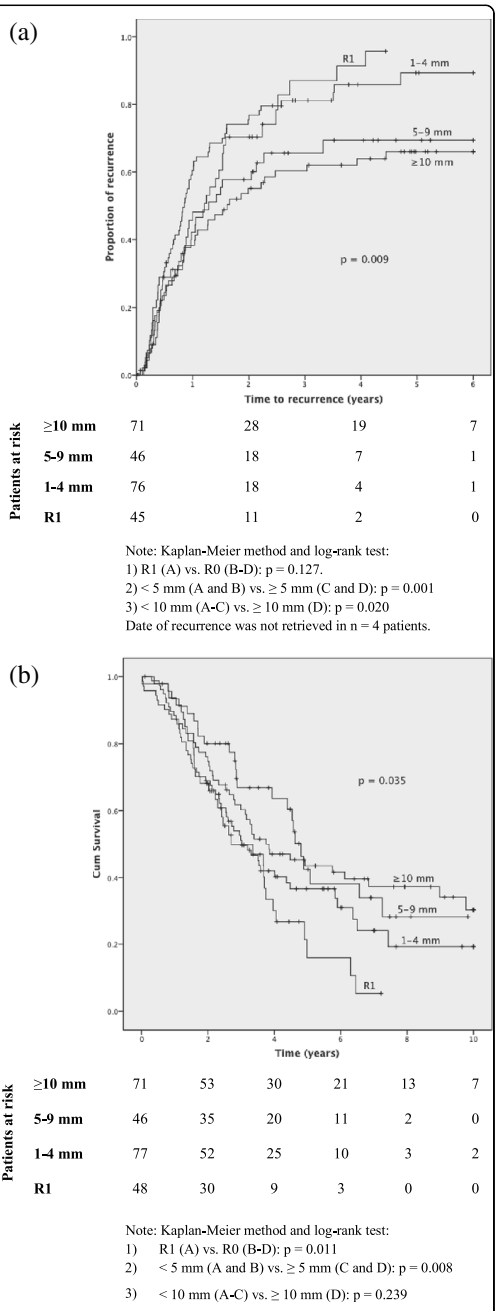

Figure 1 Time to recurrence (a) and overall survival (b) according to resection margins in n = 242 patients with primary resection for colorectal liver metastases.

model ($P = 0.067$), along with age, ASA score, number of metastases, size of the metastases and repeated resections (Table 4). When using the RM sub-groups (A to D) in the Cox model ($P = 0.111$) and the RMs as a continuous variable ($P = 0.099$), significance was not reached. We neither found any substantial differences in OS with a cut-off margin of 5 mm ($P = 0.194$). We also applied multiple fractional polynomials in the Cox regression model without identifying any non-linear relationships between RMs and OS. When adjusting for patients offered preoperative chemotherapy, multivariate analyses revealed RMs still to be a borderline significant factor predicting adverse OS ($P = 0.081$). However, in contrast to the rest, there was an adverse effect on OS of R1 vs. R0 in the downstaging group (test of interaction $P = 0.020$), adjusting for the same variables as listed in Table 4. No such effect was evident in the perioperative group.

Finally, we conducted survival calculations according to the site of recurrence and the involvement of LR independently of RMs. We could not reveal any difference in five-year OS between LR (total), hepatic-only and extrahepatic recurrence ($P = 0.947$). Patients with LR only proved a better five-year OS compared to patients with recurrence at other sites (35.9% vs. 25.4%, $P = 0.048$). Within the latter group we neither found any substantial differences in OS ($P = 0.130$).

Discussion

The main finding in this study was that positive RMs influenced overall survival after resection for CLM. LR occurred more frequently and TTR was shorter in RMs <5 mm. Following preoperative chemotherapy, negative margins were still a prerequisite for achieving an improved survival.

Our study demonstrated that positive margins were related to a more dismal prognosis. This is consistent with the majority of other comparable reports [1,9,24-26]. Even with a consensus on obtaining free margins after liver resections there are still conflicting results about the sufficient magnitude of the RMs and its impact on recurrence and survival. Several studies have shown that local recurrence and survival were independent of the extent of the free margins [8,9,11,27]. In addition to the benefit of R0, we found an increasing OS and TTR in patients with RMs >5 mm (Figures 1a and b). No additional advantage was found for free RMs beyond this limit. In the report from Nuzzo *et al.* a RM ≤5 mm was associated with a greater risk of LR, as well as reduced disease-free survival

Table 4 Results from Cox regression analysis of resection margins and other factors affecting overall survival in 253 patients after primary resection for colorectal liver metastases

			Overall survival					
			Univariate			Multivariate		
Variable		n	HR	95% CI	*P*	HR	95% CI	*P*
Age/10 y		253	1.32	(1.12, 1.54)	<0.001	1.29	(1.08, 1.54)	0.005
DFI, months		253	0.91	(0.80, 1,03)	0.122	0.91	(0.79, 1.05)	0.187
Number of metastases		253	1.19	(1.10, 1.28)	<0.001	1.31	(1.17, 1.45)	<0.001
Metastasis diam, cm		242	1.11	(1.03, 1.19)	0.006	1.09	(1.02, 1.18)	0.023
RM status	R0	205	1.00	Reference		1.00	Reference	
	R1	48	1.69	(1.14, 2.51)	0.014	1.53	(0.98, 2.39)	0.067
T stage					0.931			0.897
	T2	25	1.00	Reference		1.00	Reference	
	T3	180	1.10	(0.65, 1.87)		0.99	(0.54, 1.81)	
	T4	34	1.11	(0.57, 2.19)		0.88	(0.40, 1.90)	
N stage					0.506			0.229
	N0	91	1.00	Reference		1.00	Reference	
	N1	103	1.19	(0.83, 1.72)		1.32	(0.88, 1.98)	
	N2	51	1.27	(0.81, 1.98)		1.49	(0.92, 2.42)	
ASA score		253	1.62	(1.20, 2.19)	0.002	1.61	(1.13, 2.29)	0.009
Bilobar	No	159	1.00	Reference		1.00	Reference	
	Yes	94	1.38	(1.01, 1.89)	0.048	1.22	(0.80, 1.86)	0.353
Re-resections			0.78	(0.60, 1.01)	0.045	0.71	(0.52, 0.97)	0.016

HR, hazard ratio; CI, confidence interval; DFI, disease-free interval (time between resection of the primary tumor in the colon or rectum and the detection of hepatic metastases); RM, resection margin; T and N stage, analysis of primary tumor in colon or rectum; ASA, American Society of Anesthesiologists. Unknown T-stage n = 14, unknown N-stage: n = 8, unknown diameter of metastases: n =11.

(DFS) and OS [13]. Likewise, Vandeweyer *et al.* demonstrated that a RM >1 mm improved OS. However, a margin beyond 1 mm did not yield any detectable advantage in survival [28]. In a large series of 2,715 prospective collected patients Hamady *et al.* stated that 1 mm free margin was sufficient to obtain a five-year DFS of 33%. An extra margin width did not provide DFS advantage in this study [29]. Konopke *et al.* showed that even though the size of the RMs did not affect overall survival, a resection margin below 3 mm increased hepatic and overall recurrence [30]. Wray *et al.* found that RM <1 cm was a powerful factor in increasing the risk for local and distant recurrence as well as DFS [31]. The result was, however, not confirmed in a multivariate setting when only R0 cases were included.

Several studies have through genetic techniques detected tumour DNA up to 4 mm from the tumour border, and thereby determining a rational basis for the extent of surgical excision [12,32-34]. We also demonstrated that RMs plays a key role in the development of LR independently of recurrence in other sites of the liver and/or extrahepatic (Tables 2 and 3) using multinomic logistic regression. Furthermore, no correlation was detected between RMs and intra- or extrahepatic relapse without LR involvement (Table 3). Surprisingly, we detected an increased risk for extrahepatic recurrence in patients with less than 5 mm free margins. We have no plausible explanation for this finding, and the results may suggest that RMs might be surrogates of the extent of the disease. This is also visualized through a fairly high level of recurrence (89.4%) in the group B (1 to 4 mm, Figure 1), as 40.3% of these patients had extrahepatic recurrence (Table 2). We hypothesise that intra- or extrahepatic relapse (without LR involvement) is based on progression of preoperatively non-detectable micro-metastases and not the impact of RMs. Unlike our report, de Haas *et al.* found that R1 was associated with intrahepatic recurrence, whereas no difference in surgical margin recurrence was seen between R0 and R1 [14]. Likewise, in the multi-institutional study of 1,669 patients by de Jong *et al.*, R1 resection was associated with intrahepatic recurrence, whereas extrahepatic disease developed independently of margin status [3].

In the study by Are *et al.* the RMs were analysed as a continuous variable [35]. They found no difference in survival between positive margins and sub-centimetre resections ($P = 0.31$) in the multivariate analysis, whereas patients with RM >1 cm had a significantly improved outcome. Nevertheless, the authors observed a favourable survival in sub-centimetre R0 resections, and they concluded that these patients should not be denied hepatic resections.

In some published articles, with initially marginally or non-resectable CLM receiving preoperative chemotherapy, the important role of free margins were found to be less important [14-16]. In the current study, we found an improved OS for R0 vs. R1 in patients receiving preoperative chemotherapy. Our data indicates that R0 resections should be strived for in these patients. This finding also corresponds with recently published studies [36,37]. In patients with initially unresectable metastases successfully treated with chemotherapy, positive margins predicted in the univariate model an adverse outcome ($P = 0.017$), but this finding was not evident in resectable patients offered perioperative chemotherapy ($P = 0.502$). In the multivariate analysis this difference was confirmed. In the first group, postoperative chemotherapy was administered more rarely (17.5%) compared with the latter group (69.8%). In other settings like stage III colon cancer, adjuvant chemotherapy regimens have proved to expose and reduce the recurrence rates [38,39]. We hypothesise the same mechanism in R1 patients, where adjuvant chemotherapy may suppress any remaining metastatic disease, leading to an increase in TTR and OS. This resembles the trial by Tranchart *et al.* [37].

An exact measurement of RMs is impeded by the application of surgical devices such as the ultrasonic aspirator, harmonic scalpel, and Kelly clamp-crushing technique, which removes a small rim of liver tissue during the transection. An overestimation of R1 cases might be the consequence [9,14]. Likewise, the invasive irregular growth pattern in liver metastases, combined with a rough transection surface, makes the histological examination less reliable in narrow margins. The increasing use of chemotherapy may also complicate the measurement of RMs due to a more irregular surface, as reported by Ng *et al.* [34].

Several studies have demonstrated an effect of R1 resections on OS in univariate analyses, but have not confirmed this finding in a multivariate setting [9,13,35]. This result has led to a discussion whether R status is a surrogate of other biologic factors such as size, number, growth patterns and distribution of the metastases, rather than an independent predictor for adverse outcome. In the current trial R1 was of borderline significance in the multivariate analysis ($P = 0.067$). However, a more advanced disease in patients undergoing R1 vs. R0 resection is reflected by a higher incidence of bilobar distribution and number of metastases. This is consistent with other recognized reports [9,14,35]. The advancement of disease reflected in number and size of metastases appears to have greater impact on survival than RMs. Based on our findings we advocate that R0 should be performed despite no clear significance in the Cox model. We also assume with a larger number of patients in the cohort, the significance might be obtained.

We reported a rather high incidence of LR (total) and global recurrence of 40 (16.5%), and 175 (72.3%) patients,

respectively, which is somewhat higher than other studies [9,12,13]. The RMs (groups A to D) did not influence the TTR when patients with LR (total) were excluded from the analysis ($P = 0.097$). A similar finding in TTR was evident between R1/R0 ($P = 0.403$). However, we could neither detect any worse OS in patients with LR (total) compared with patients with recurrence at other sites. A fairly high proportion of patients with LR were offered repeated resections with curative intent. In patients with LR only, 78.6% underwent a second resection, following better OS compared with recurrence in other sites. We could not obtain a different OS among patients with relapse in other localisations. Despite a high recurrence rate, we have obtained a five-year OS of nearly 40% and a median OS of 45 months. We assume an aggressive multimodal treatment and with repeated resections in patients with advanced disease and marginally resectable metastases may be justified despite the high number of relapse [14]. Based on this, patients with suspected narrow RMs should not be excluded from resection for colorectal liver metastases.

Conclusions

A positive resection margin predicted adverse OS after resection for colorectal liver metastases. Likewise, local recurrence and time to recurrence were influenced by positive margins. In addition, an increasing survival rate, a reduced recurrence (local and global) rate and a longer time to recurrence were seen in patients with RM >5 mm, but could not be verified beyond this extent. In an era with expanding use of chemotherapy, our study supports that R0 resections are still important in order to obtain the best outcome in patients treated with resection for colorectal liver metastases.

Abbreviations

CEA: carcinoembryonal antigen; CLM: colorectal liver metastases; CT: computed tomography; DFS: disease-free survival; LR: local recurrence; OS: overall survival; RM: resection margin; TTR: time to recurrence.

Competing interests

The authors declare that they have no competing interests. There was no grant support for this study.

Authors' contributions

All the authors have fulfilled the ICMJE guidelines, according substantial contribution to this study. JHA has been in charge of the data collection. All the authors have participated in the design, acquisition, data analysis and interpretations. GEE is a medical statistician, and has been in charge of the statistical calculations and interpretations of the collected data. All the authors have contributed in the drafting and have revised the manuscript critically before submission. They have all given their final approval of this version to be published, and take full responsibility for all the aspects and results in this manuscript.

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Author details

[1]Department of Acute and Digestive Surgery, Haukeland University Hospital, N-5021 Bergen, Norway. [2]Department of Clinical Medicine, University of Bergen, N-5020 Bergen, Norway. [3]Department of Research and Development, Centre for Clinical Research, Haukeland University Hospital, N-5021 Bergen, Norway. [4]Department of Global Public Health and Primary Care, University of Bergen, N-5020 Bergen, Norway.

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Predictive factors for time to recurrence, treatment and post-recurrence survival in patients with initially resected colorectal liver metastases

Jon-Helge Angelsen[1,2*], Asgaut Viste[1,2], Inger Marie Løes[3,6], Geir Egil Eide[4,5], Dag Hoem[1], Halfdan Sorbye[3,6] and Arild Horn[1]

Abstract

Background: Despite progress in resection for colorectal liver metastases (CLM), the majority of patients experience recurrence. We aimed to evaluate factors influencing time to recurrence (TTR), treatment and post-recurrence survival (PRS) related to site of recurrence.

Methods: This is a retrospective population-based cohort study (1998–2012) of consecutive patients without extrahepatic disease treated with resection for CLM in a referral centre.

Results: A total of 311 patients underwent resection for CLM. After a median follow-up of 4.2 years (range 1.2–15.2), 209 (67.4 %) patients developed recurrence, hepatic 90, extrahepatic 59 and both 60. Median TTR was 14.0 months, and 5-year recurrence-free status was 25.7 %. Five- and 10-year overall survival (OS) was 38.8 and 22.0 %, respectively. Median OS was 45 months. A multivariate analysis displayed synchronous disease (hazard ratio (HR) 1.50), American Society of Anaesthesiologists (ASA) score (HR 1.40), increasing number (HR 1.24) and size of metastases (HR 1.08) to shorten TTR (all $p < 0.05$). Perioperative chemotherapy ($n = 59$) increased overall TTR (HR 0.63) and overall survival (OS; HR 0.55). Hepatic TTR was correlated to synchronous disease (HR 2.07), number of lesions (HR 1.20), R1 resection (HR 2.00) and ASA score (HR 1.69), whereas extrahepatic TTR was correlated to N stage of the primary (HR 1.79), number (HR 1.27) and size of metastases (HR 1.16). Single-site recurrence was most common (135 of 209, 64.5 %), while 58 patients had double- and 16 triple-site relapses. Median PRS was 24.3 months. There was a difference in median PRS (months) according to site of relapse: liver 30.5, lung 32.3, abdominal 22.0, liver and lung 14.3, others 14.8 ($p = 0.002$). Repeated liver resections were performed in $n = 57$ patients resulting in 40.6 months median OS and 36.8 % 5-year OS.

Conclusions: An adverse overall TTR was correlated to number and size of metastases, ASA score and synchronous disease. Perioperative chemotherapy increased TTR and OS after surgery for CLM. Patients with solitary post-resection relapse in the liver or lungs had the potential for longevity due to multimodal treatment.

Keywords: Resection colorectal liver metastases, Overall survival, Time to recurrence, Sites of recurrence, Perioperative chemotherapy, Post-recurrence survival

* Correspondence: jon-helge.angelsen@helse-bergen.no
[1]Department of Acute and Digestive Surgery, Haukeland University Hospital, N-5021 Bergen, Norway
[2]Department of Clinical Medicine, University of Bergen, Bergen, Norway
Full list of author information is available at the end of the article

Background

Surgical intervention (resection or local ablation) is the only potentially curative option for patients with colorectal liver metastases (CLM). Due to progress in surgical technique and perioperative care during the last two decades, perioperative morbidity (17–38 %) and mortality (1–2 %) have declined [1–3]. Furthermore, by multimodal treatment like chemotherapy, radiofrequency ablation (RFA) and portal vein embolization, some patients have achieved downsizing of initially unresectable CLM and might be offered a potentially curative resection [4]. Perioperative chemotherapy has also improved progression-free survival [5] and overall survival (OS) in the adjuvant setting [6]. Following these advancements, OS has increased to 47–58 % in several series [3, 7, 8]. Despite this, the recurrence rates (57–77 %) and disease-free survival have remained almost unchanged in the same period [7, 9–11]. Due to improved surgical approach, repeated resections are more often offered to selected patients with recurrent disease [12, 13]. For patients beyond the range of cure, optimal oncological therapy may yield life extension [14, 15].

A large number of reports have evaluated survival after resection, whereas rather few studies have highlighted the fate of patients with recurrence according to site of relapse.

In this paper, we aimed to analyse the (1) sites of recurrence after liver resections for CLM, (2) factors influencing time to recurrence (TTR) in different sites and (3) treatment of post-resection recurrence and the impact on survival according to site of relapse.

Methods

This is a population-based retrospective cohort study with a consecutive series of patients with CLM treated at Haukeland University Hospital, Norway (1998–2012). The data were retrospectively recorded from 1998 to 2008 and prospectively from 2009 to 2012. The unit is the only hepato-pancreato-biliary centre in the region, which makes this a population-based cohort from this catchment area of 0.7 million people. Clinical data were retrieved from the patients' medical records. All patients were prospectively followed up until 15 March 2014. Recorded variables were TNM stage and site of primary tumour, synchronous metastases (detected within 3 months after resection of the primary colorectal tumour [16, 17]), time between resection of primary tumour and diagnosis of liver metastases (disease-free interval), number and size of metastases, chemotherapy (indication, number of cycles and response), American Society of Anaesthesiologists (ASA) score, date of liver resection, resection margins (R1 <1 mm [8]), complications (Clavien-Dindo classification [18]), in-hospital mortality, time to recurrence, sites of recurrence and death (perioperative, cancer-related and other causes) and last date of follow-up for survivors.

Preoperative assessments

The selection criteria for surgery were a sufficient tumour-free liver remnant (>30 %) and absence of (a) disseminated disease as evaluated preoperatively and/or (b) non-resectable extrahepatic metastases. Patients with preoperatively detected resectable extrahepatic disease and macroscopically incomplete resection (R2) were excluded from further analyses (Fig. 1). Preoperative investigations included computed tomography (CT) scan of the chest and abdomen/pelvis and tumour marker analysis (carcinoembryonic antigen (CEA)). In cases with an inconclusive CT scan, magnetic resonance imaging (MRI) of the liver, contrast-enhanced ultrasound and/or ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan were performed. Each patient was finally discussed in a multidisciplinary team setting.

Chemotherapy

Perioperative chemotherapy was given in 59 cases. Forty-six patients were initially considered unresectable

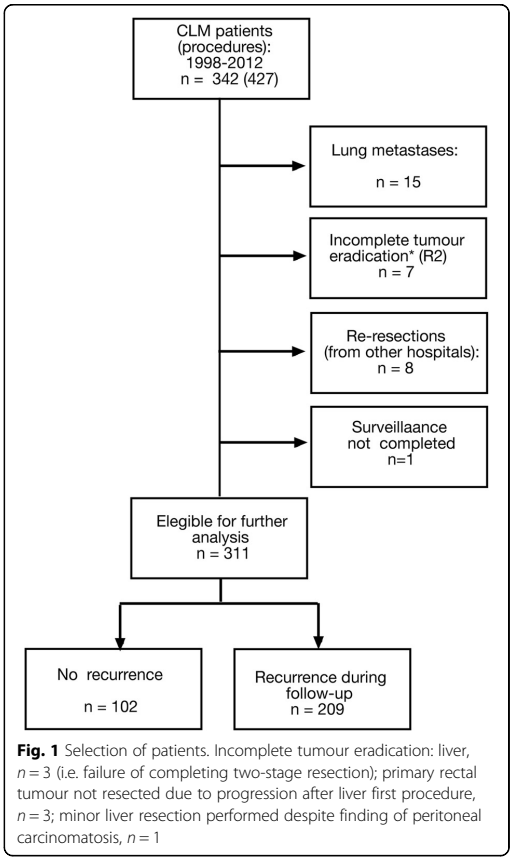

Fig. 1 Selection of patients. Incomplete tumour eradication: liver, $n = 3$ (i.e. failure of completing two-stage resection); primary rectal tumour not resected due to progression after liver first procedure, $n = 3$; minor liver resection performed despite finding of peritoneal carcinomatosis, $n = 1$

and underwent downsizing chemotherapy. Seven patients developed CLM while on adjuvant chemotherapy after resection for stage III colon cancer. The Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1 was applied to evaluate the efficiency of chemotherapy [19]. The size of the metastases was measured on CT scan by dedicated radiologists. All patients in the perioperative group received treatment with FOLFOX regimen (fluorouracil, leucovorin and oxaliplatin) with intended six cycles before and after surgery. The indications for perioperative chemotherapy have changed during the study period. A total of 17 patients were enrolled in the European Organisation for Research and Treatment of Cancer (EORTC) multicentre study 40983 in the period 2001–2004 [5]. Later on, perioperative chemotherapy given as Nordic FLOX [20] were offered to patients <76 years with Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and no previous treatment with oxaliplatin. In the downsizing group, patients were treated with a variety of chemotherapy regimens. First-line treatment with Nordic FLOX or Nordic FLIRI regimen was most commonly used [15, 20] optionally in combination with endothelial growth factor receptor (EGFR) inhibitors (if *KRAS* wild type) or angiogenesis inhibitors.

Surgical procedures

Surgical techniques included intraoperative ultrasonography, repeated inflow control (Pringle manoeuvre) and transection using Ultracision, Kelly clamp, Cavitron Ultrasonic Surgical Aspirator (CUSA) or Ultrasonic Aspirator (Olympus Sonosurg™). Throughout the period, we have intended to obtain a parenchyma sparing approach with wedge resections whenever possible. Formal resections (hemihepatectomies or lobectomies) were reserved for metastases abutting the portal triad or the hepatic veins. To increase intended complete tumour eradication, intraoperative RFA (StarBurst®) and portal vein ligations/embolization with two-stage resections were performed. Simultaneous colorectal cancer surgery was reserved for healthy patients with colon cancer and less advanced CLM. Further details are listed in Table 1.

Surveillance

Follow-up after surgery included CT scan of the chest, abdomen and pelvis every 3 months for the first 2 years, and thereafter every 6 months for the next 3 years. After completing the 5-year follow-up, survival data were retrieved from the medical record and the Norwegian National Registry. Patients that died from other causes were also included in the analysis of OS but were censored in the estimation of TTR according to the definition stated by Punt et al. [21].

Table 1 Clinical characteristics

Variable, statistics	Estimate
Age in years, median (range)	66.1 (22.8, 91.3)
Gender males/females—ratio	169/142
Location primary tumour	
Colon, *n* (%)	205 (65.9)
Rectum, *n* (%)	101 (32.5)
Combined, *n* (%)	5 (1.6)
Synchronous metastases[a], *n* (%)	157 (50.5)
Disease-free interval[b] in months, median (range)	4.2 (−11, 131)
Resections, *n*	311
Hemihepatectomy/lobectomy, *n* (%)	137 (44.1)
Wedge/segment resections, *n* (%)	174 (55.9)
Simultaneous radio frequency ablation, *n* (%)	12 (3.9)
Two-stage resections with PVL, *n* (%)	3 (1.0)
Simultaneous colorectal cancer surgery, *n* (%)	18 (5.8)
R1 resections (<1 mm)	63 (20.3)
Extent of RM in millimeter, median (range)	4 (0–50)
Number of metastases, median (range)	2 (1, 12)
Metastases diameter in centimeter, median (range)	3.0 (0.2, 15.0)
Bilobar metastases, *n* (%)	108 (34.7)
Number of procedures/patient (1/2/3/4/5)	254/42/11/3/1
Morbidity (Clavien-Dindo score 1/2/3/4/5)	19/28/52/5/6
Outcome of chemotherapy (RECIST criteria)	
Partial response, *n* (%)	63 (56.2)
Stable disease, *n* (%)	42 (37.5)
Progression, *n* (%)	5 (4.4)
Unknown, *n* (%)	2 (1.8)

Unknown Clavien-Dindo score $n = 1$
RM resection margin, *RECIST* Response Evaluation Criteria in Solid Tumour version 1.1
[a]Synchronous metastases: detection of liver metastases within 3 months after primary colorectal resection
[b]Disease-free interval: time between resection of the primary colorectal tumour and detection of CLM

Statistical analysis

Variables with possible impact on TTR and OS like size and number of metastases, resection margins, synchronous disease and TNM stage of primary tumour were analysed with univariate and multivariate survival methods [22]. The exact chi-square (χ^2) test was used for categorical variables, the t test and the one-way analysis of variance for normally distributed variables, and the Mann-Whitney U test and the Kruskal-Wallis test for non-normally distributed continuous variables. Univariate analyses of TTR and OS were estimated by the Kaplan-Meier method [23] and tested for significance with the log-rank test [24]. Multivariate analyses of risks for overall, hepatic and extrahepatic TTR were performed as Cox proportional hazards regression reporting hazard ratios (HR) and 95 % confidence intervals (CI)

[25] A p value ≤0.05 was considered significant. OS was defined as time to death irrespective of cause, and TTR was defined as the interval between resection and the detection of relapse [21]. The analyses were performed using SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) and Stata 13 statistical software (StataCorp, College Station, TX, USA). We decided to use TTR rather than disease-free survival as an outcome in assessing recurrence patterns, since the latter has treatment-related and non-cancer-related deaths as endpoints [21].

Ethics

The regional committee for medical and health research ethics, western Norway approved the study, with an exemption to the requirement for obtaining informed consent from patients included in the retrospective part (1998 to 2008). In the prospective part (2009 to 2012), patients were enrolled through written consent.

Results

A total of 342 patients were resected for CLM of whom 311 were eligible for further analysis. Patient selection and characteristics are outlined in Fig. 1 and Table 1, respectively.

Patterns and sites of recurrence

After a median follow-up of 4.2 years (range 1.2–15.2) 209 patients (67.4 %) developed recurrence. The sites of recurrence were distributed between hepatic ($n = 90$), extrahepatic ($n = 59$) and both locations ($n = 60$). Further details are outlined in Fig. 2. Median TTR was 14.0 months, and 5-year recurrence-free status was 25.7 %. Single-site relapse was most common (135 of 209, 64.5 %), while 58 patients had double- and 16 triple-site relapses. TTR was associated with number and size of metastases, synchronous disease, increasing ASA score and perioperative chemotherapy in the multivariate analysis (Tables 2 and 3). Hepatic TTR correlated with synchronous CLM, ASA score, R1 resections and number of metastases. Extrahepatic TTR (including hepatic/extrahepatic) corresponded with node positive of the primary, number and size of metastases. Positive margins and synchronous disease were insignificant. The sites of recurrence were independent on the primary tumour location (colon vs. rectum) both in univariate and multivariate analyses.

Chemotherapy

The clinical characteristics of patients undergoing downsizing or perioperative chemotherapy vs. surgery alone are described in Table 4. Forty-five patients completing perioperative chemotherapy experienced a longer median TTR (19.1 months) compared with patients who aborted this treatment ($n = 14$, 10.8 months), downsizing chemotherapy ($n = 46$, 10.4 months), surgery alone ($n = 199$, 14.4 months) or adjuvant chemotherapy after resection of the primary ($n = 7$, 4.6 months), $p = 0.005$. Five-year recurrence-free status for these groups was 43.2, 30.8, 19.5, 23.7 % and none, respectively, ($p = 0.005$, Fig. 3). TTR was different between patients with response, stable disease and progression, with a 5-year recurrence-free status of 35.3, 26.0 % and none, respectively ($p = 0.021$). Positive margins influenced TTR in responders to chemotherapy where 3-year recurrence-free status in R0 and R1 was 47.8 and 7.1 % and median TTR was 2.0 and 0.4 years, respectively ($p < 0001$). This difference was not evident in patients with stable disease. For this group, 3-year recurrence-free status was 30.4 % in R0 whereas all patients with R1 had recurrence within 3 years. Median TTR was 1.1 and 1.5 years, respectively ($p = 0.756$). Perioperative chemotherapy correlated to an increased overall TTR in the multivariate analysis (Tables 2 and 3). Five- and 10-year OS with perioperative chemotherapy vs. surgery alone was 57.0 and 31.6 % vs. 37.1 and 20.0 %, respectively ($p = 0.024$). Median OS in the same groups was 73 and 43 months, respectively. This finding was also confirmed in a multivariate analysis (HR 0.55 [0.34, 0.89], $p = 0.014$). Patients completing perioperative regimen had an improved 5- and 10-year OS of 62.0 and 51.6 %, respectively.

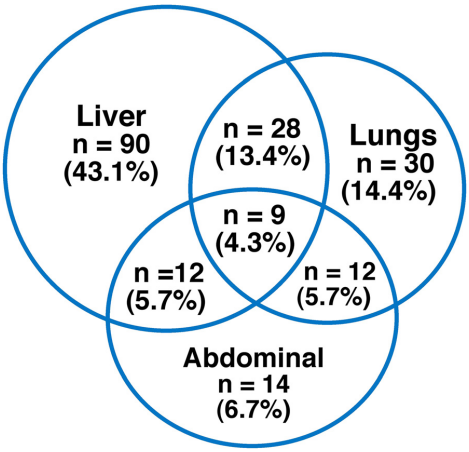

Fig. 2 Patterns of recurrence in the three most common sites in $n = 209$ patients. Note: Other sites and combinations of recurrence: cerebral only, $n = 1$; liver/bones, $n = 2$; liver/cerebral, $n = 1$; lungs/cerebral, $n = 2$; liver/lungs/cerebral, $n = 1$; liver/abdominal/bones, $n = 2$; liver/lungs/bones, $n = 4$; liver/ovary $n = 1$. Recurrence was not detected in $n = 101$ patients with a median observation time of 4.2 years. Definitions: *Abdominal* locoregional recurrence involving peritoneal, lymph node and local recurrence

Table 2 Cox regression analysis of factors affecting time to overall recurrence

		Overall recurrence (TTR)					
		Univariate			Multivariate		
Variable	*n*	HR	95 % CI	*p*	HR	95 % CI	*p*
Age/10 years	311	1.11	(0.98, 1.26)	0.113	1.08	(0.94, 1.25)	0.253
Synch. mets							
No	154	1.00	Reference	0.002	1.00	Reference	0.010
Yes	157	1.65	(1.25, 2.17)		1.50	(1.10, 2.04)	
No. of mets	311	1.21	(1.14, 1.30)	<0.001	1.24	(1.14, 1.34)	<0.001
Mets diam (cm)	311	1.11	(1.04, 1.18)	0.002	1.08	(1.01, 1.16)	0.022
RM status							
R0	246	1.00	Reference	0.013	1.00	Reference	0.143
R1	63	1.53	(1.11, 2.11)		1.30	(0.92, 1.84)	
ASA score (1–3)	311	1.28	(1.00, 1.65)	0.054	1.40	(1.05, 1.87)	0.022
Clavien-Dindo	311	1.12	(1.01, 1.25)	0.037	1.07	(0.95, 1.20)	0.267
N-pos[a]							
No	190	1.00	Reference	0.058	1.00	Reference	0.091
Yes	109	1.32	(0.99, 1.78)		1.30	(0.96, 1.77)	
Chemotherapy							
None	199	1.00	Reference	0.010	1.00	Reference	0.014
Periop.	59	0.71	(0.49, 1.05)		0.63	(0.42, 0.95)	
Downsiz.	46	1.31	(0.90, 1.89)		0.93	(0.62, 1.39)	
Adj. colon[b]	7	2.98	(1.31, 6.79)		2.80	(1.21, 6.48)	

Unknown N status $n = 12$. Unknown RM $n = 2$
RM resection margins, *HR* hazard ratio, *CI* confidence interval
[a]N-pos: positive lymph nodes of the primary tumour in colon or rectum
[b]Adj. colon: adjuvant chemotherapy after surgery for stage III (node positive) colon cancer

Post-recurrence survival (PRS)

Median PRS was 24.3 months and differed according to sites of relapse; liver 30.4; lungs 33.1; abdominal 22.0; liver and lungs 14.3; other combinations 14.8 months as outlined in Fig. 4 ($p = 0.002$). Five-year PRS in these groups was 23.9, 16.4, 8.7, 4.1 and 13.6 %, respectively. Median PRS was related to the number of recurrence sites; one site 28.8; two 16.8; three 13.5 months ($p = 0.001$). Hepatic re-resections were performed in $n = 57$ cases, whereas 9 patients had resections of emerging lung metastases. The number of recurrence sites correlated with a secondary surgical resection ($p < 0.001$). Of 90 patients with sole hepatic recurrence, 48 underwent resection, 20 chemotherapy, 6 RFA and 9 patients best supportive care. Data were not available in 7 patients. Median PRS (months) varied between these groups; resection 50.0; chemotherapy 15.2; RFA 19.9; best supportive care 5.3 ($p < 0.001$). Patients with combined recurrence in the liver and lungs underwent resection in 5 of 28 (17.8 %) cases.

Overall survival

Three-, 5- and 10-year OS after the first hepatic resection were 58.8, 38.8 and 22.0 %, respectively. Median OS was 45 months. During follow-up, 17 non-CLM-related deaths were observed (other malignant disease $n = 2$; cardiac disease $n = 4$; other liver disease $n = 2$; miscellaneous $n = 9$). Five-year OS after the second liver resection was 36.8 % and median OS 40.6 months.

Discussion

Single-site hepatic and pulmonic recurrences were most common after surgery for CLM. Positive resection margins, number of metastases and synchronous disease were associated with hepatic recurrence, whereas number and size of metastases and positive primary nodal status were correlated with extrahepatic recurrence. Perioperative chemotherapy increased TTR and OS as well. Patients with single-organ recurrence in the lungs or liver were offered re-resections and/or supplementary chemotherapy had an extended survival.

About two thirds experienced recurrence after hepatic resection with the liver as the most common site (43 %) which is fairly consistent with other reports [7, 9, 10]. Positive margins were associated with hepatic TTR, supporting previous series from de Jong et al. where R1

Table 3 Cox regression analysis of factors affecting time to hepatic and extrahepatic recurrence

	Hepatic recurrence			Extrahepatic recurrence[a]		
	Multivariate					
Variable	HR	95 % CI	*p*	HR	95 % CI	*p*
Age/10 years	1.00	(0.81, 1.24)	0.995	1.14	(0.95, 1.37)	0.165
Synch. mets						
No	1.00	Reference	0.002	1.00	Reference	0.499
Yes	2.07	(1.28, 3.33)		1.15	(0.77, 1.73)	
No. of mets	1.20	(1.07, 1.35)	0.005	1.27	(1.14, 1.41)	<0.001
Mets diam (cm)	0.99	(0.88, 1.10)	0.828	1.16	(1.07, 1.27)	0.001
RM status						
R0	1.00	Reference	0.010	1.00	Reference	0.769
R1	2.00	(1.20, 3.31)		0.93	(0.57, 1.52)	
ASA score						
(1–3)	1.69	(1.08, 2.64)	0.021	1.24	(0.85, 1.81)	0.264
Clavien-Dindo	0.99	(0.83, 1.19)	0.958	1.12	(0.96, 1.30)	0.165
N-pos						
No	1.00	Reference	0.652	1.00	Reference	0.007
Yes	0.90	(0.58, 1.41)		1.79	(1.16, 2.76)	
Chemotherapy						
None	1.00	Reference	0.143	1.00	Reference	0.036
Periop.	0.63	(0.34, 1.18)		0.64	(0.37, 1.11)	
Downsiz.	1.36	(0.78, 2.39)		0.63	(0.35, 1.14)	
Adj. colon	2.28	(0.54, 9.60)		3.12	(1.10, 8.84)	

Unknown N status $n = 12$. Unknown RM $n = 2$
RM resection margins, *HR* hazard ratio, *CI* confidence interval
[a]Extrahepatic recurrence also included combined hepatic and extrahepatic recurrence

resection was predictive for hepatic recurrence (HR 1.36) [7]. In a former publication, we also demonstrated a correlation between R1 resections and local recurrence [26]. In cases with synchronous disease, sole hepatic post-resection recurrence may indicate an underestimation of tumour advancement due to preoperatively undetected liver lesions. A limitation in our cohort is the lack of routinely performed preoperative MRI. Several series have shown this modality to be more accurate than CT scan [27–30]. With the evolvement of efficient cytotoxic regimens, MRI may also yield additional information in cases of CT-verified complete response [30]. Primary nodal status indicated a high risk for extrahepatic recurrence. This represents most probably a more aggressive clinical course with undetected systemic disease at the time of liver surgery. A recent study by Lee et al. detected a significant distributive variation in metastatic pattern, concatenating a rectal primary with extrahepatic recurrence, and a colon primary with hepatic recurrence, respectively [31]. No such association was verified in the present study.

The indication for perioperative chemotherapy is still reported as controversial [32]. The EORTC intergroup trial 40983 demonstrated an increase in progression-free survival in patients undergoing perioperative chemotherapy [5], especially in patients with CEA above 5.0 [33]. However, after a long-term follow-up, no significant benefit was obtained in OS [34]. The current study observed a significant improvement in overall TTR for the perioperative chemotherapy group compared with resection only. This finding was not significant in the site-specific recurrence analysis (Tables 2 and 3), most probably due to an insufficient number of patients. Data from the EORTC trial also demonstrated a reduction in

Table 4 Clinical characteristics in $n = 304$ patients with no chemotherapy, perioperative and downsizing chemotherapy in conjunction with resection for colorectal liver metastases

Variable	No chemo ($n = 199$)	Perioperative ($n = 59$)	Downsizing ($n = 46$)	*p*
No. of mets (mean/median)	2.1/1	2.4/2	3.4/3	0.001[a]
Mets size (cm, median)	3.5/3	2.8/2.1	4.1/3.5	0.003[a]
Age (year, mean/median)	65.9/66.5	63.7/65.1	62.0/63.6	0.055[b]
R1 (*n*, %)	40 (20.2)	12 (20.7)	10 (21.7)	0.973[c]
N-pos primary (*n*, %)	68 (36.0)	19 (32.8)	21 (46.7)	0.311[c]
Clavien-Dindo (1–5)	61 (31.3)	24 (41.4)	16 (35.6)	0.350[c]
ASA (1/2/3)	20/136/43	5/50/4	2/34/10	0.069[c]
Synch. mets (*n*, %)	71 (35.7)	36 (61.0)	30 (65.2)	0.001[c]
Gender (M/F)	104/95	36/23	26/20	0.475[c]
Recurrence pattern (*n*, A/B)	53/82	15/18	20/15	0.256[c]

Seven of 311 patients had progress on chemotherapy after stage III colon cancer, not included in the analysis
A hepatic recurrence, *B* extrahepatic recurrence
[a]Kruskal-Wallis test
[b]One-way analysis of variance
[c]χ^2 test

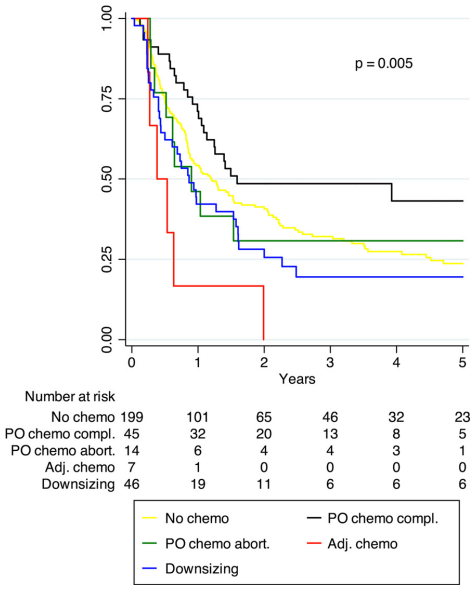

Fig. 3 Time to recurrence according to different chemotherapy regimens. *PO chemo compl* perioperative chemotherapy completed, *Adj. chemo* adjuvant chemotherapy after stage III colon cancer (lymph node positive) with progression of liver metastases. Log-rank test: No chemo vs. PO chemo completed, $p = 0.045$; No chemo vs. downsizing chemo, $p = 0.155$

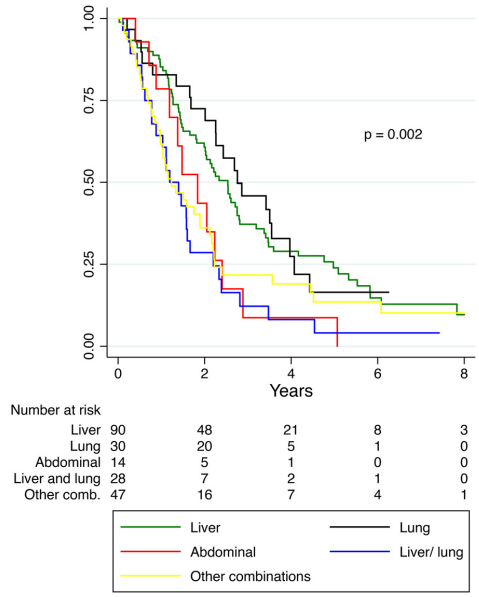

Fig. 4 Post-recurrence survival according to sites of relapse. Log-rank test: recurrence in lung vs. liver, $p = 0.586$; liver vs. abdominal, $p = 0.040$; liver vs. liver/lung, $p = 0.010$; liver vs. other combinations, $p = 0.012$

hepatic relapse following perioperative FOLFOX regimen [35]. In our cohort, patients in the perioperative group had more advanced clinical course like synchronous disease and increased number of metastases compared to patients with resection only. Positive margins influenced TTR in cases with response ($p < 0.0001$) as opposed to patients with stable disease ($p = 0.756$). In responders after chemotherapy, tumour shrinkage may lead to remaining therapy-resistant islets of malignant cell clusters near the main lesion as well as an irregular surface which may cause local recurrence in cases with narrow or positive margins [36]. Furthermore, we detected a significantly better 5-year OS in the chemotherapy group, with a 5-year OS of 62 % in patients completing chemotherapy, as opposed to other reports [37, 38]. However, our results should be interpreted with caution due to possible selection bias and a heterogeneous cohort mainly retrospectively observed.

Patients in the downsizing group presented an insignificant difference in the univariate ($p = 0.155$) and multivariate analysis in overall, hepatic and extrahepatic TTR compared with the surgery alone group (Fig. 3 and Tables 2 and 3) despite more adverse tumour load (Table 4). These results support a previous study by Adam et al. [4]. Patients offered resection after progression while on adjuvant chemotherapy after stage III colon surgery demonstrated a short median TTR of 4.6 months. Based on this finding in this small group of patients, surgery may not be beneficial [39].

We demonstrated that PRS was correlated to the site of recurrence. Single-organ lesions in the lungs or liver appeared to have the best outcome. A high proportion of repeated hepatic resections increased the PRS in patients with hepatic recurrence. Five-year OS of 36.8 % after the second resection was comparable to the survival rates after the first resection (5-year OS 38.8 %). A similar survival rate has been demonstrated in several other studies [12, 13, 40]. The use of repeated liver resections varies in the literature. Assumpcao et al. [11] and D'Angelica et al. [9] performed a second resection in 28 and 30 % of the cases with recurrence, respectively, whereas Mise et al. [10] conducted metastasectomy in 85 % of isolated hepatic or lung recurrence. Despite unresectable lesions in the lung, nearly 3-year median survival was observed in the present cohort. This finding may also justify the expanding criteria for liver resection in selected patients with unresectable lung metastases [41]

Conclusions

Sites of recurrence predict the outcome after surgery for CLM. Resection margins, number of metastases and synchronous disease were associated with hepatic

recurrence, whereas N positive (primary tumour), number and size of metastases were associated with extrahepatic recurrence. Perioperative chemotherapy prolonged TTR and increased OS significantly. Patients with single-organ relapse have the potential for longevity due to multimodal treatment with repeated resections and supplementary chemotherapy.

Abbreviations

ASA: American Society of Anaesthesiologists; CLM: colorectal liver metastases; HR: hazard ratio; OS: overall survival; PRS: post-recurrence survival; RFA: radio frequency ablation; TTR: time to recurrence.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All the authors have fulfilled the ICMJE guidelines, according to substantial contribution to this study. JHA has been in charge of the data collection. All the authors have participated in the design, acquisition, data analysis and interpretations. GEE is a medical statistician and has been in charge of the statistical calculations and interpretations of the collected data. All the authors have contributed in the drafting and have revised the manuscript critically before submission. They have all given their final approval of this version to be published and take full responsibility for all the aspects and results in this manuscript.

Author details

[1]Department of Acute and Digestive Surgery, Haukeland University Hospital, N-5021 Bergen, Norway. [2]Department of Clinical Medicine, University of Bergen, Bergen, Norway. [3]Department of Oncology, Haukeland University Hospital, Bergen, Norway. [4]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway. [5]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway. [6]Department of Clinical Science, University of Bergen, Bergen, Norway.

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III

Original article

Population-based study on resection rates and survival in patients with colorectal liver metastasis in Norway

J.-H. Angelsen[1,4], A. Horn[1], H. Sorbye[2,5], G. E. Eide[3,6], I. M. Løes[2,5] and A. Viste[1,4]

[1]Department of Acute and Digestive Surgery, [2]Department of Oncology and [3]Centre for Clinical Research, Department of Research and Development, Haukeland University Hospital, and Departments of [4]Clinical Medicine, [5]Clinical Science and [6]Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Correspondence to: Dr J.-H. Angelsen, Department of Acute and Digestive Surgery, Haukeland University Hospital, N-5021 Bergen, Norway (e-mail: jon-helge.angelsen@helse-bergen.no)

Background: Detailed knowledge about the proportion of patients with colorectal liver metastases (CLM) undergoing resection is sparse. The aim of this study was to analyse cumulative resection rates and survival in patients with CLM.

Methods: For this population-based study of patients developing CLM during 2011–2013, data were extracted from the Norwegian Patient Registry and the Cancer Registry of Norway.

Results: A total of 2960 patients had CLM; their median overall survival was 10·9 months. Liver resection was performed in 538 patients. The cumulative resection rate was 20·0 per cent. The cumulative resection rate was 23·3 per cent in patients aged less than 40 years, 31·1 per cent in patients aged 40–59 years, 24·7 per cent in those aged 60–74 years, 17·9 per cent in those aged 75–79 years and 4·7 per cent in patients aged 80 years or more ($P < 0·001$). In multivariable analysis, resection rate was associated with age, extrahepatic metastases, disease-free interval and geographical region. Overall survival after diagnosis of CLM was affected by liver resection (hazard ratio (HR) 0·54, 95 per cent c.i. 0·34 to 0·86), rectal cancer (HR 0·82, 0·74 to 0·90), metachronous disease (HR 0·66, 0·60 to 0·74), increasing age (HR 1·32, 1·28 to 1·37), region, and extrahepatic metastases (HR 1·90, 1·74 to 2·07). Three- and 4-year overall survival rates after hepatectomy were 73·2 and 54·8 per cent respectively.

Conclusion: The cumulative resection rate in patients with CLM in Norway between 2011 and 2013 was 20 per cent. Resection rates varied across geographical regions, and with patient and disease characteristics.

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Introduction

Colorectal cancer is the second most common malignancy in Norway with approximately 4000 patients diagnosed annually[1]. A substantial proportion of patients with colorectal cancer (15–29 per cent) develop colorectal liver metastases (CLM), and surgery is the only treatment with curative intent[2–5]. Improvements in surgical technique, better insight into the biology of the disease, and the development of potent chemotherapeutic and targeted drugs have expanded the indications for surgery[6–8]. Numerous single-centre studies have reported good outcomes in patients undergoing CLM resection[4]. However, most studies are from tertiary referral institutions. Hence, the results could be distorted by selection bias and aggressive oncological treatment algorithms. In patients denied surgery, oncological treatment has prolonged survival for up to 2–3 years after the diagnosis of CLM[9–11]. Until recently, information on resection rates in patients with CLM was limited[2,3,12–14].

Treatment of colorectal cancer in Norway is governed by public hospitals with obligations to the health authorities in the reporting of newly diagnosed cases and treatment of cancer. The present study aimed to analyse resection rates and overall survival in patients with synchronous and metachronous CLM.

Methods

Norway has four regional health authorities covering a population of 5·2 million people: North (0·48 million), Central (0·7 million), West (1·1 million) and South-East

Table 1 Baseline characteristics at diagnosis in 2960 patients with colorectal liver metastases in Norway, 2011–2013

	Total ($n = 2960$)	Unresected ($n = 2422$)	Resected ($n = 538$)‡
Age (years)*	70·8 (22·8–104·2)	72·3 (22·1–104·2)	66·1 (22·8–91·1)
< 40	53 (1·8)	42 (79)	11 (21)
40–59	504 (17·0)	362 (71·8)	142 (28·2)
60–74	1276 (43·1)	987 (77·4)	289 (22·6)
75–79	421 (14·2)	356 (84·6)	65 (15·4)
≥ 80	706 (23·9)	675 (95·6)	31 (4·4)
Sex ratio (M : F)	1666 : 1294	1341 : 1081	325 : 213
Site of tumour			
Colon	2138 (72·2)	1795 (84·0)	343 (16·0)
Rectum	822 (27·8)	627 (76·3)	195 (23·7)
Extrahepatic metastases	1282 (43·3)	1159 (90·4)	123 (9·6)
Lung metastases	680 (23·0)	647 (26·7)	33 (6·1)
Disease-free interval			
Synchronous	706 (23·9)	666 (94·3)	40 (5·7)
Early metachronous (≤ 1 year)	1620 (54·7)	1274 (78·6)	346 (21·4)
Late metachronous (> 1 year)	634 (21·4)	482 (76·0)	152 (24·0)
Region†			
South-East	1604 (54·2)	1338 (83·4)	266 (16·6)
West	604 (20·4)	472 (78·1)	132 (21·9)
Central	444 (15·0)	357 (80·4)	87 (19·6)
North	307 (10·4)	254 (82·7)	53 (17·3)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). Median follow-up was 2·6 years among survivors. †Region unknown for one patient. ‡Nine patients in the resection group underwent radiofrequency ablation only.

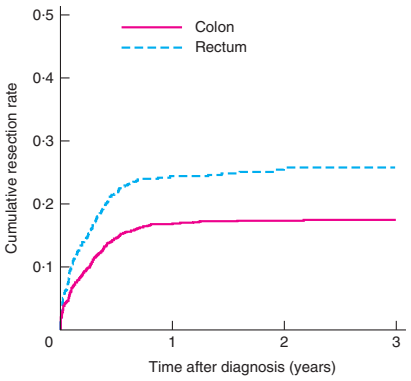
(2·9 million). Hepatobiliary centres are located in each region. During past decades there has been centralization of the diagnosis, treatment and surveillance of patients with colorectal cancer. Resection of colonic and rectal cancer is performed in 31 and 20 hospitals respectively (more than 10 resections per year)[15]. All patients with newly diagnosed CLM are intentionally referred to multidisciplinary team meetings at the regional hepatopancreatobiliary (HPB) centres for evaluation of whether surgery is indicated.

The Regional Ethics Committee of Western Norway Health Authority approved the study in March 2015.

Registry data

Data from the Norwegian Patient Registry (NPR) and the Cancer Registry of Norway (CRN) were extracted and synchronized. Diagnoses and procedures were classified according to the ICD-10 and the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical/Medical Procedures (NCSP/NCMP) respectively. The Norwegian Directorate of Health (Helsedirektoratet) governs the NPR. Acquisition of patient-identifiable data has been undertaken since 2008, with registration of diagnoses and procedures (NCMP) for all patients treated in Norwegian public hospitals or outpatient clinics. From 2011, the registration also included dates of surgical procedures (NCSP/NCMP). Financial reimbursement for procedures depends on registration in the NPR. Most high-volume centres have employed controllers to maintain accurate coding. Data extracted from the NPR for the present database included diagnosis of the primary tumour (C18–20), metastases (C77–79) and liver resections (NCSP code JJB). Patients with a code for liver metastases (C78·7) but without registration of any procedure (JJB) were assumed to be ineligible or unfit for surgery.

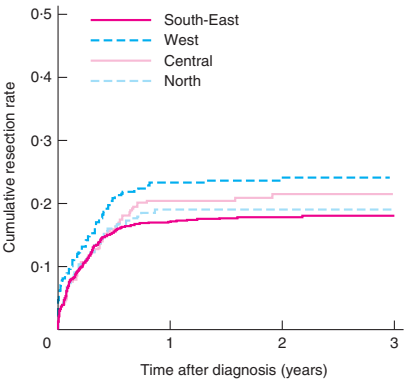
All Norwegian hospitals are obliged by law to report all cancer diagnoses to the CRN. Patients with a diagnosis of colorectal cancer were extracted from the registry for the years 2011–2013. The CRN provides data with a completeness of 98·8 per cent and morphological verification of 93·8 per cent[16]. Stage of disease at diagnosis and location of the primary tumour were also retrieved from the CRN. The CRN lacks complete data on surgical procedures, organ-specific metastases and metachronous disease. Data from the CRN are based on reports from pathology laboratories as well as from clinical departments. Data from the CRN and NPR were further synchronized through the unique patient identification number, and finally merged with data from the Norwegian National Registry (Folkeregisteret) that added supplementary information regarding county affiliation and vital status (alive or dead). The time span between diagnosis of the primary tumour and registration of metastases was defined as the disease-free interval (DFI), and further stratified into synchronous (DFI 0), early metachronous (1 year or less)



No. at risk

Colon	2137	(335)	1177	(6)	560	(1)	0
Rectum	820	(188)	408	(5)	199	(0)	0

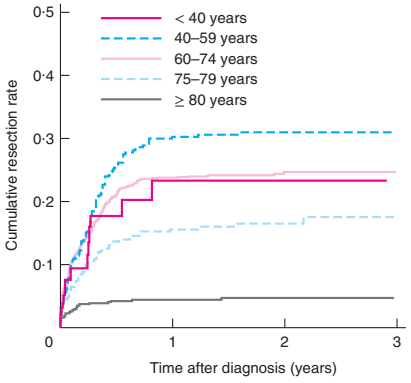
a Primary tumour



No. at risk

South-East	1602	(256)	909	(7)	430	(1)	0
West	603	(129)	283	(2)	146	(0)	0
Central	444	(85)	241	(2)	120	(0)	0
North	307	(53)	151	(0)	62	(0)	0

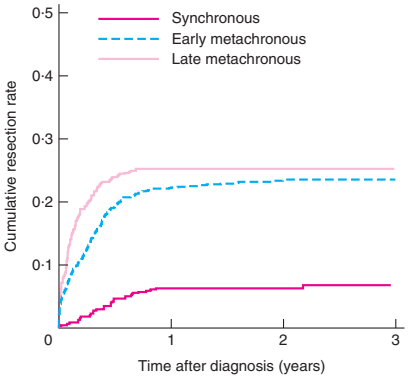
b Region



No. at risk

< 40	53	(11)	19	(0)	10	(0)	0
40–59	502	(137)	232	(3)	123	(0)	0
60–74	1275	(283)	655	(5)	304	(0)	0
75–79	421	(62)	227	(2)	104	(1)	0
≥ 80	706	(30)	452	(1)	218	(0)	0

c Age



No. at risk

Synchronous	706	(39)	450	(0)	212	(1)	0
Early metachronous	1617	(332)	832	(11)	400	(0)	0
Late metachronous	634	(152)	303	(0)	147	(0)	0

d Disease-free interval

Fig. 1 Cumulative resection rates for 2960 patients with colorectal liver metastases (CLM) in Norway, 2011–2013, according to **a** primary tumour, **b** geographical region, **c** age and **d** disease-free interval for patients with synchronous, early (1 year or less) or late (more than 1 year) metachronous CLM, adjusted for death as a competing risk. For the at-risk data, numbers of failure events are shown in parentheses. Data were missing for three patients. **a,c,d** $P < 0{\cdot}001$, **b** $P = 0{\cdot}019$ (log rank test)

and late metachronous (more than 1 year) metastases[17]. Patients with appendiceal cancer (C18·1) were excluded, owing to the morphological diversity in this group (carcinoid, gastrointestinal stromal tumour, adenocarcinoma and pseudomyxoma peritonei). The date of last follow-up was 19 June 2015.

Statistical analysis

Overall survival was estimated by the Kaplan–Meier method[18] and groups were compared with the log rank test[19]. Cumulative resection rates were estimated and adjusted for mortality as a competing event by retaining deceased subjects in the risk set to the end of follow-up, and by plotting 1 minus Kaplan–Meier survival curves[20]. Cox regression analysis was used to evaluate cumulative resection rates in patients with CLM[21,22]. For overall survival in patients with CLM, liver resection was included as a time-dependent co-variable to avoid immortal time bias[23]. $P \leq 0{\cdot}050$ was considered statistically significant. Analyses were performed using SPSS® version 22 (IBM, Armonk, New York, USA) and Stata® version 14 (StataCorp, College Station, Texas, USA).

Results

Between 2011 and 2013, 3376 patients with CLM (C18–20 and C78·7) were registered in the NPR. Some 463 (13·7 per cent) were not registered in the CRN as having a diagnosis of colorectal cancer and were excluded from the analysis. Seventeen patients with appendiceal cancer were also excluded. Sixty-four patients initially registered in the NPR as having a benign primary diagnosis (diverticulitis (K57·3), benign colorectal neoplasm (D12·6–8), neoplasm of uncertain behaviour (D37) or inflammatory bowel disease (K50–52)) and liver metastases (C78·7) were also enrolled in the study as they had a histologically verified cancer diagnosis (C18–20) in the CRN. Finally, 2960 patients with CLM were registered in both the NPR and the CRN, and formed the study group.

Cumulative resection rates in patients with colorectal liver metastases

Baseline characteristics of patients with CLM (resected and unresected) are shown in *Table 1*. Median follow-up time among survivors was 2·6 (range 1·5–4·5) years. The estimated cumulative resection rate was 20·0 per cent in patients with CLM (*Fig. 1*). Twelve patients underwent surgery for CLM more than 1 year after CLM diagnosis; all were treated with chemotherapy before surgery. Factors affecting the cumulative resection rate are presented in *Fig. 1*. Patients aged 40–59 years had the highest rate of cumulative resection (31·1 per cent), whereas the rate in patients below 40 years of age was similar to that in those aged 60–74 years (23·3 and 24·7 per cent respectively). Cumulative resection rates were 17·9 per cent in those aged 75–79 years and 4·7 per cent in patients aged 80 years or more ($P < 0{\cdot}001$). No regional differences were detected in cumulative resection rates in patients aged 80 years or above ($P = 0{\cdot}963$).

Patients with rectal cancer had a significantly higher cumulative resection rate than those with colonic cancer (26·1 *versus* 17·7 per cent respectively; $P < 0{\cdot}001$). Resection in patients with synchronous CLM was less common (6·8 per cent) than in patients with early (23·7 per cent) or late (25·3 per cent) metachronous lesions ($P < 0{\cdot}001$). Liver resection was performed more often in men (21·6 per cent *versus* 17·9 per cent in women; $P = 0{\cdot}032$). Differences in cumulative resection rates were observed between the four geographical regions: South-East, 19·1 per cent; West, 24·2 per cent; Central, 21·9 per cent; North, 19·0 per cent ($P = 0{\cdot}019$). Univariable and multivariable analyses are shown in *Table 2*. Age, region, DFI and extrahepatic metastases were independently associated with the probability of liver resection.

Overall survival of patients diagnosed with colorectal liver metastases

Median overall survival after detection of CLM was 10·9 months. The 1-, 3- and 4-year overall survival rates were 47·7, 24·4 and 19·1 per cent respectively. Factors associated with survival were analysed in univariable and multivariable Cox models with liver resection as a time-dependent co-variable (*Table 3*).

Age was statistically significantly associated with outcome following the diagnosis of CLM. The 3-year survival rate was 34 per cent (median 21·0 months) in patients aged less than 40 years, 35·4 per cent (22·5 months) in patients aged 40–59 years, 28·8 per cent (14·4 months) in patients aged 60–74 years, 18·4 per cent (8·1 months) in those aged 75–79 years, and 11·6 per cent (3·6 months) in patients aged 80 years or more ($P < 0{\cdot}001$).

Overall survival after CLM diagnosis was higher in the Western region compared with the South-East (reference) region (HR 0·86, 95 per cent c.i. 0·77 to 0·96). Overall survival in the two other regions (North and Central) did not differ significantly compared with the reference.

The 3-year survival rate was significantly different according to DFI: 15·2 per cent (median 6·3 months) in patients with synchronous disease, 28·1 per cent

Table 2 Cox regression analysis of time to resection in 2960 patients with colorectal liver metastases diagnosed in Norway, 2011–2013

	Univariable		Multivariable	
	Hazard ratio	*P*	Hazard ratio	*P*
Age (years)		< 0·001		< 0·001
< 40	0·67 (0·36, 1·23)		0·69 (0·37, 1·28)	
40–59	1·00 (reference)		1·00 (reference)	
60–74	0·85 (0·70, 1·04)		0·78 (0·63, 0·95)	
75–79	0·60 (0·45, 0·80)		0·56 (0·41, 0·75)	
≥ 80	0·19 (0·13, 0·28)		0·17 (0·12, 0·25)	
Sex (F *versus* M)	0·87 (0·73, 1·04)	0·122	0·94 (0·75, 1·07)	0·503
Region		0·085		0·039
South-East	1·00 (reference)		1·00 (reference)	
West	1·30 (1·05, 1·60)		1·31 (1·06, 1·61)	
Central	1·17 (0·92, 1·49)		1·21 (0·95, 1·55)	
North	1·03 (0·77, 1·38)		0·94 (0·70, 1·26)	
Tumour site		< 0·001		0·056
Colon	1·00 (reference)		1·00 (reference)	
Rectum	1·40 (1·17, 1·66)		1·19 (1·00, 1·43)	
Disease-free interval*		< 0·001		< 0·001
Synchronous†	1·00 (reference)		1·00 (reference)	
Early metachronous (≤ 1 year)	3·72 (2·68, 5·16)		3·66 (2·63, 5·09)	
Late metachronous (> 1 year)	4·96 (3·50, 7·02)		6·95 (4·88, 9·91)	
Extrahepatic metastases	0·40 (0·33, 0·49)	< 0·001	0·31 (0·25, 0·38)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Time from detection of primary tumour to diagnosis of liver metastases; †liver metastases detected at time of diagnosis of primary tumour.

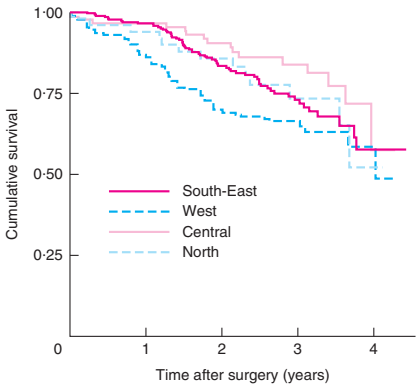
Table 3 Time-dependent Cox model for survival after detection of liver metastasis in 2960 patients with liver metastases in Norway, 2011–2013

	Univariable		Multivariable	
	Hazard ratio	*P*	Hazard ratio	*P*
Liver resection*	0·45 (0·28, 0·71)	< 0·001	0·54 (0·34, 0·86)	0·004
Age (/10 years)	1·32 (1·74, 1·37)	< 0·001	1·32 (1·28, 1·37)	< 0·001
Sex		0·038		0·314
M	1·00 (reference)		1·00 (reference)	
F	1·09 (1·01, 1·19)		1·05 (0·96, 1·14)	
Region		0·107		0·026
South-East	1·00 (reference)		1·00 (reference)	
West	0·88 (0·79, 0·98)		0·86 (0·77, 0·96)	
Central	0·95 (0·84, 1·08)		0·89 (0·79, 1·01)	
North	0·91 (0·79, 1·05)		0·95 (0·83, 1·10)	
Tumour site		< 0·001		< 0·001
Colon	1·00 (reference)		1·00 (reference)	
Rectum	0·76 (0·69, 0·84)		0·82 (0·74, 0·90)	
Disease-free interval†		< 0·001		< 0·001
Synchronous‡	1·00 (reference)		1·00 (reference)	
Metachronous (≤ 1 year)	0·63 (0·57, 0·69)		0·66 (0·60, 0·74)	
Metachronous (> 1 year)	0·75 (0·67, 0·85)		0·68 (0·60, 0·78)	
Extrahepatic metastases	1·70 (1·56, 1·85)	< 0·001	1·90 (1·74, 2·07)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Calculated as a time-dependent predictor in the Cox model; †time from detection of primary tumour to diagnosis of liver metastases; ‡liver metastases detected at time of diagnosis of primary tumour.

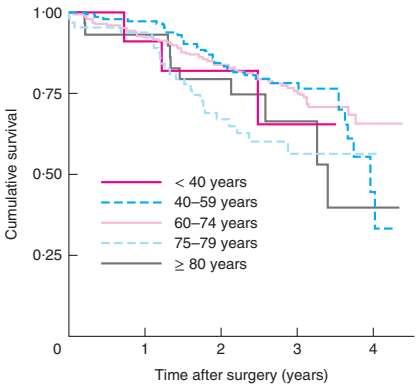
(14·7 months) in patients with early metachronous CLM, and 25·4 per cent (9·4 months) in those with late metachronous CLM ($P < 0·001$). These differences were confirmed on multivariable analysis ($P < 0·001$) (*Table 3*). Patients with rectal cancer and CLM had an improved outcome compared with those with colonic cancer; the 3-year survival rate was 28·3 per cent (median 16·1 months) *versus* 22·9 per cent (9·4 months) respectively ($P < 0·001$).

Surgery for CLM almost halved the risk of death (HR 0·54; $P = 0·004$) compared with that in patients with



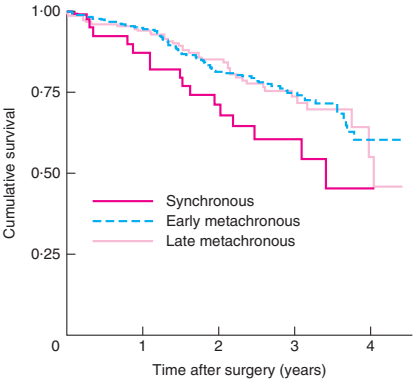
No. at risk									
South-East	260	(9)	251	(32)	163	(15)	69	(7)	10
West	131	(18)	113	(20)	71	(3)	39	(3)	6
Central	86	(3)	83	(5)	67	(4)	32	(4)	4
North	50	(3)	47	(4)	33	(4)	15	(2)	1

a Region



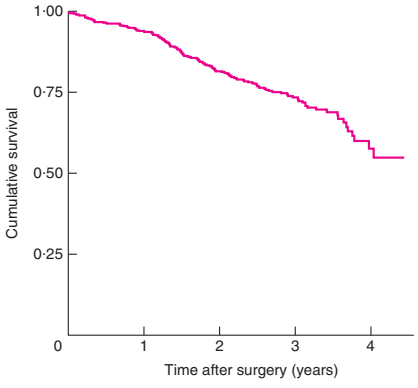
No. at risk									
< 40	11	(1)	10	(1)	7	(1)	1	(0)	0
40–59	141	(4)	137	(17)	94	(6)	48	(7)	4
60–74	283	(22)	261	(23)	182	(13)	86	(7)	13
75–79	63	(4)	59	(16)	33	(4)	15	(0)	2
≥ 80	29	(2)	27	(4)	18	(2)	5	(2)	2

b Age



No. at risk									
Synchronous	39	(5)	34	(6)	21	(3)	11	(2)	1
Early metachronous	339	(19)	320	(42)	215	(12)	103	(10)	14
Late metachronous	149	(9)	140	(13)	98	(11)	41	(4)	6

c Disease-free interval



No. at risk									
	527	(33)	494	(61)	334	(26)	155	(16)	21

d All patients

Fig. 2 Overall survival after 527 resections for colorectal liver metastases (CLM) in Norway, 2011–2013, according to **a** region, **b** age and **c** disease-free interval for patients with synchronous, early (1 year or less) or late (more than 1 year) metachronous CLM, and **d** for all patients (unstratified). For the at-risk data, numbers of failure events are shown in parentheses. Data were missing for 11 patients. Survival analysis was not performed in nine patients undergoing radiofrequency ablation. **a** $P = 0{\cdot}038$, **b** $P = 0{\cdot}054$, **c** $P = 0{\cdot}068$ (log rank test)

unresected CLM. In patients with CLM not eligible for resection (2422), 1-, 3- and 4-year survival rates were 37·2, 13·8 and 9·0 per cent respectively. The median survival was 7·3 months. Nine patients in the resection group underwent radiofrequency ablation only.

Survival after resection of liver metastases

During the 3-year study interval, a total of 538 patients underwent liver resection. One-, 3- and 4-year survival rates after first liver resection were 93·6, 73·2 and 54·8 per cent respectively. Median survival was not reached. The 30-day mortality rate was 0·9 per cent (5 patients). A statistically significant difference in survival was observed between the regions (*Fig. 2*). In Cox regression analysis of survival after resection of CLM, only geographical region was found to be an independent predictor ($P = 0{\cdot}037$).

Discussion

In this study, the cumulative resection rate in patients diagnosed with CLM in Norway between 2011 and 2013 was 20·0 per cent. Resection rates varied between geographical regions, and were higher in patients aged 40–59 years, in patients with metachronous disease and in those with rectal cancer. Liver resection doubled the likelihood of survival in patients with CLM. Finally, age was not a significant predictor of outcome following resection of CLM.

Improvements in surgical skill and oncological treatment have led to an increasing proportion of patients being offered CLM resection, with acceptable postoperative morbidity[24,25]. The selection criteria for surgery have expanded, and patients with limited concomitant extrahepatic disease are now also offered surgery[26–28]. Several region-based studies[2–4,12] have published resection rates for CLM, with values between 6 and 35 per cent. Three nationwide studies have been conducted in recent years. In a British population-based study[29], the rate of liver resection was 2·7 per cent among patients previously operated on for colorectal cancer. The resection rate varied with geographical region[29]. No information on resection rates according to the incidence of CLM was given. In 2015, van der Geest and colleagues[13] presented data from a Dutch registry comprising patients with synchronous CLM (1996–2011), of whom 18 per cent underwent liver resection during the last part of the study interval. Analysis of data from the Swedish Cancer Registry for synchronous CLM showed a 17·8 per cent resection rate[30]. Limitations of the last two studies were the lack of data on patients with metachronous disease. In the present study, a cumulative resection rate of 20·0 per cent was calculated for synchronous and metachronous CLM combined. A lower resection rate (6·8 per cent) was observed in patients with synchronous disease compared with rates found by van der Geest and co-workers[13] and Norèn *et al.*[30]. The results of the present study are in line with those in the 2006 French study by Manfredi and colleagues[31], who performed resections in 6·3 per cent of patients with synchronous CLM and in 16·9 per cent of those with metachronous CLM. The term synchronous was defined in the present study as metastases detected at or before diagnosis of the primary tumour, according to the recommendations of a recent consensus report[17]. Other studies have defined synchronous as CLM diagnosed within 3 months[32] or 6 months[33,34]. This may explain differences in resection rates owing to the assumption of more advanced disease in patients with a shorter DFI. Patients in the present study with early (1 year or less) or late (more than 1 year) metachronous disease had no significant difference in cumulative resection rate (23·7 *versus* 25·3 per cent respectively). After liver resection no significant difference was found when patients with synchronous, early or late metachronous CLM were considered separately, in contrast to the finding with synchronous *versus* metachronous disease. This is consistent with other reports[35].

Age was an independent predictor of liver resection, with the highest cumulative resection rate in patients aged 40–59 years. The relatively lower resection rate among patients aged less than 40 years may be due to a more advanced tumour load at the time of diagnosis. Vatandoust and co-workers[36] found that a higher proportion of younger patients (age below 40 years) with colorectal cancer presented with synchronous metastatic disease compared with older age groups. de Haas and colleagues[37] observed that younger patients (less than 40 years of age) with CLM undergoing liver resection had a more advanced tumour load at the time of surgery than those aged more than 40 years, as reflected by T and N categories. They also showed that young age (less than 40 years) was an independent predictor of poor progression-free survival after surgery. Less than 5 per cent of patients aged above 80 years underwent resection of CLM. Three-year overall survival after resection for this group was 66·4 per cent[37]. Data from a Nordic registry study[38] showed that improvements during past decades in the outcome of patients with metastatic colorectal cancer were seen mainly in younger patients, probably due to less aggressive treatment of elderly patients. In the 2008 study of Schiffmann *et al.*[39], who looked at surgical treatment of elderly patients with colorectal cancer, long-term survival was associated with stage of disease, adjuvant or palliative treatment, but not age. Other studies[40,41] also found that survival after surgery for

CLM was not associated with age, with 3-year survival rates in patients aged above 75 years of 57 and 64 per cent, comparable to the present report. Based on these findings, there may be some reluctance to perform surgery for CLM in elderly patients; probably, a higher proportion of patients in this older age group are eligible for surgical intervention.

Variation in cumulative resection rates was observed between the four geographical regions in Norway. This may be explained by different referral practices from local hospitals to the tumour board at the HPB centres. Krell and colleagues[42] described a wide variation in surgical referral patterns among American medical oncologists treating patients with CLM. Jones and co-workers[43] and Young *et al.*[44] also showed that a considerable number of patients with CLM did not undergo assessment by liver specialists. Some 63 and 29 per cent respectively of patients deemed to have unresectable disease by non-specialist liver surgeons were considered potentially resectable by the liver tumour board at the referral centre. Differences in the definition of resectability among centres may also explain disparities in resection rates. The West region was the only health trust with a significantly higher cumulative resection rate compared with the reference region (South-East). Survival after resection was lower in the West compared with that in the South-East region. However, the West region had the best survival when all patients with CLM were included. An increased resection rate may lead to reduced overall survival in the resection cohort, but ultimately increases the overall survival of the whole group of patients with CLM. However, despite a statistically significant difference in survival owing to the large number of patients included in the study, differences between the four regions may not be of great clinical importance.

Rectal cancer was also associated with an increased cumulative resection rate and survival. During the past two decades, implementation of national treatment strategies in rectal cancer has provided a better outcome for patients with rectal cancer compared with that in patients with colonic cancer[45]. It is usually surgeons who perform follow-up of these patients, whereas general practitioners do the follow-up after resection of colonic cancer, according to national guidelines. Improvements in diagnostic and treatment algorithms along with postoperative surveillance might therefore explain the increased resection and survival rates of patients with rectal cancer.

The 4-year survival rate in the present study of 54·8 per cent for patients who had liver resection is comparable with other registry reports[30]. Data on repeat liver resections were not retrieved, but are estimated to be around 18–28 per cent[8,46]. Surgery for CLM nearly halved the risk of death in the time-dependent multivariable analysis. This is similar to the European Organization for Research and Treatment of Cancer CLOCC study, in which radiofrequency ablation with or without resection in combination with chemotherapy improved outcome in unresectable patients compared with chemotherapy alone[47]. However, a recent meta-analysis[48] showed no survival benefit in ten of 11 trials with intensive follow-up and treatment after potentially curative primary colorectal cancer surgery. Intensive follow-up in this particular group of patients with CLM might be of benefit because of the large repertoire of treatment options, even in unresectable disease.

The completeness of the CRN is estimated to be 98·8 per cent[16]. Unfortunately, this registry does not record complete follow-up and data on metastases after diagnosis of the primary tumour[38]. The NPR contributed data regarding diagnosis, metastases (both synchronous and metachronous) and procedures obtained from all Norwegian public hospitals during the same time period. As financial reimbursement depends on registration of the procedure, the completeness of procedure registration is likely to be high. However, NPR incidence data on primary diagnosis (C18–20) are inaccurate for colorectal cancer compared with data from the cancer registry. The incidence of colorectal cancer in the NPR exceeded that in the CRN by 3·2 per cent[49]. For only 81 per cent of the patients was there consistency in tumour site (colon, rectosigmoid junction and rectum) between the two registries. By synchronizing data from the NPR and CRN, patients registered only in the NPR were excluded from the present study. No validated survey of the metastatic data from the NPR is available. A further limitation of the study is the lack of data on diagnostic modalities (CT, MRI or PET) used to document the extent of disease, including the number, size and distribution of the CRM. These factors influence the probability of liver resection and overall survival. Information about extrahepatic disease at baseline was extracted from the diagnostic codes. Neither the NPR nor the CRN contains data on ASA fitness grades or perioperative complications. Data on recurrence after resection, for determination of progression-free survival, are also lacking. Data on follow-up after detection of CLM in patients offered palliative chemotherapy or best supportive care were not available. Comparison of the outcome of patients undergoing liver resection with that of surgery-naive patients is difficult in observational studies. It is not advisable to compare survival with Kaplan–Meier plots owing to the assumption of immortal time bias[23]. The time from detection of CLM to resection can be defined as the immortal time, extending for more than 1 year in some patients. This was overcome by using

resection as a time-dependent co-variable in a Cox model when determining outcome in patients with CLM.

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